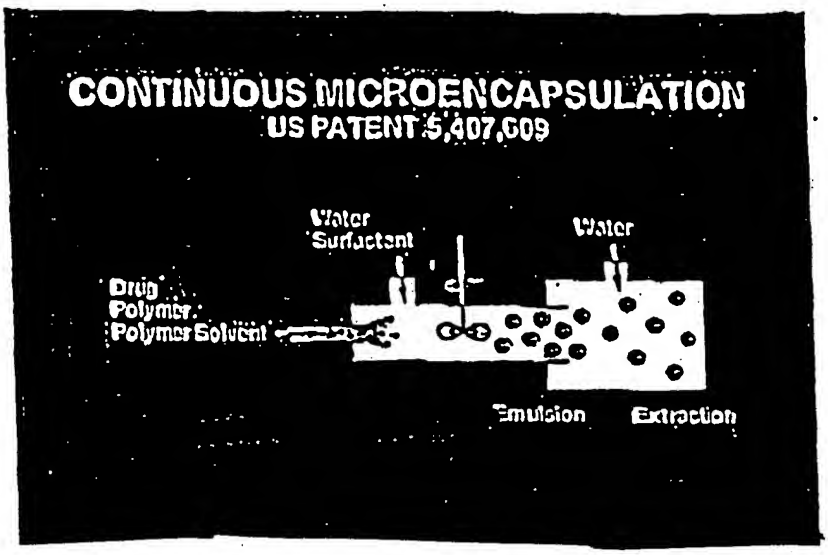
SOUTHERN RESEARCH'S PATENTED MICROENCAPSULATION PROCESS



Advantages

- US Patent issued 1995
- Fast encapsulation time -- milliseconds
- Minimal exposure to polymer solvent
- High encapsulation efficiency
- Good Yields
- Makes small microparticles
  <100 micron <10 micron

Drugs Microencapsulated

- Proteins
- Peptides
- Small molecules
- Water-soluble drugs
- Hydrophobic drugs
- Drugs encapsulated in lactide/glycolide polymers

FIGURE 1

FIGURE 2

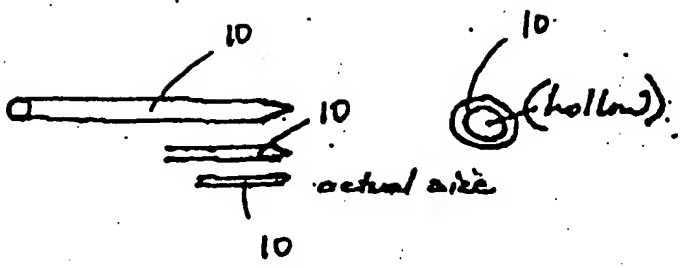
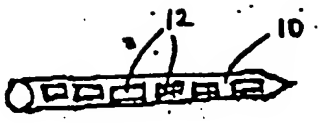


FIGURE 3



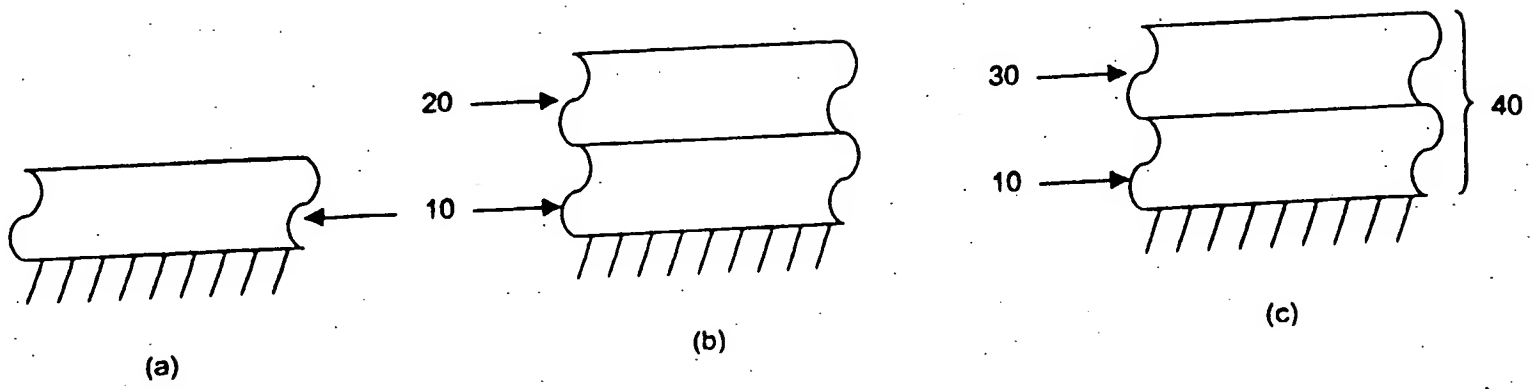


FIGURE 4

Conditions: Ambient

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Hardness:	F	B	3B	4B	F

Conditions: 5 minutes in 37°C pH 7.4 Saline Buffer

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Hardness:	F	B	9B	<9B	F

Hardness Rating: 2H-H-F-HB-B-2B-3B-4B-5B-6B-7B-8B-9B

Harder ⟷ Softer

FIGURE 5

Conditions: Ambient

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Resistance To Cracking	< 3 mm	< 3 mm	< 3mm	< 3mm	<3mm

Conditions: 5 minutes in 37°C pH 7.4 Saline Buffer

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Resistance To Cracking	< 3 mm	< 3 mm	< 3mm	< 3mm	< 3mm

FIGURE 6

Conditions: Ambient

Material:	PX510	PX261	PX749	PX125	PX510 + 14% Paclitaxel
Class:	5B	5B	5B	4B	5B

Class Rating: 5B = 0% of coating removed from substrate
4B = Less than 5% of coating removed from substrate

FIGURE 7

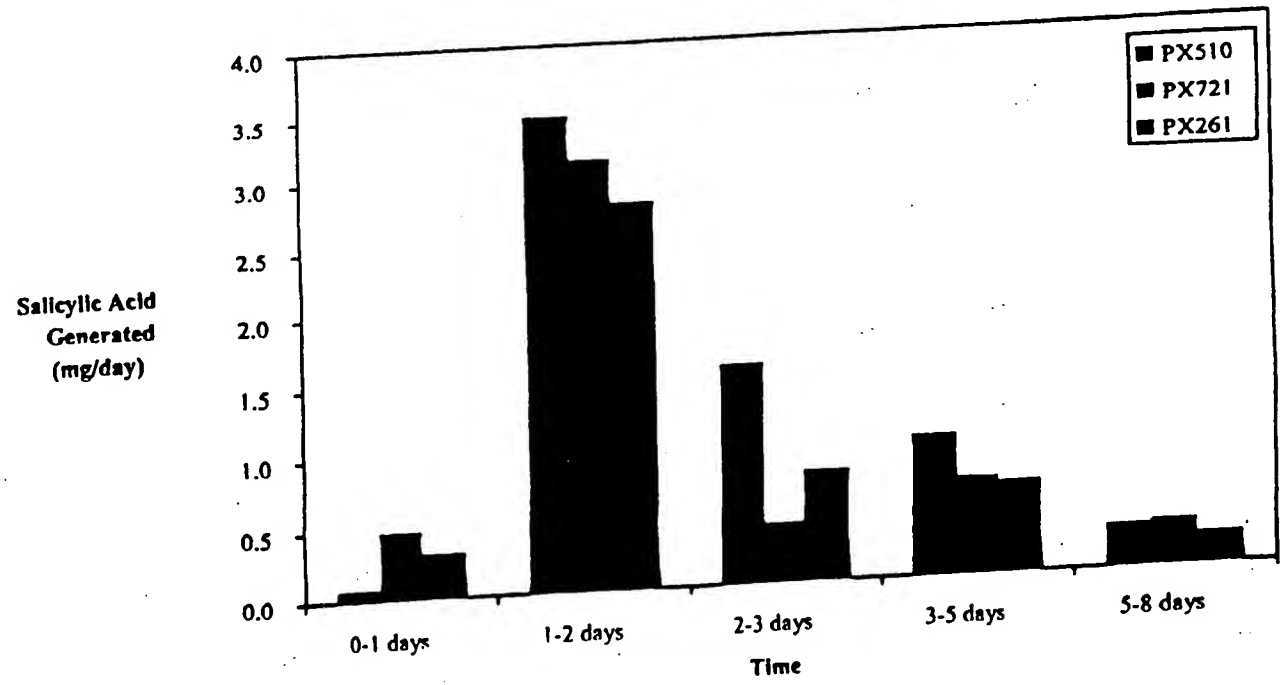

PX510
PX721
PX261
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Salicylic Acid Generated (mg/day)
0-1 days
1-2 days
2-3 days
3-5 days
5-8 days
Time

FIGURE 8

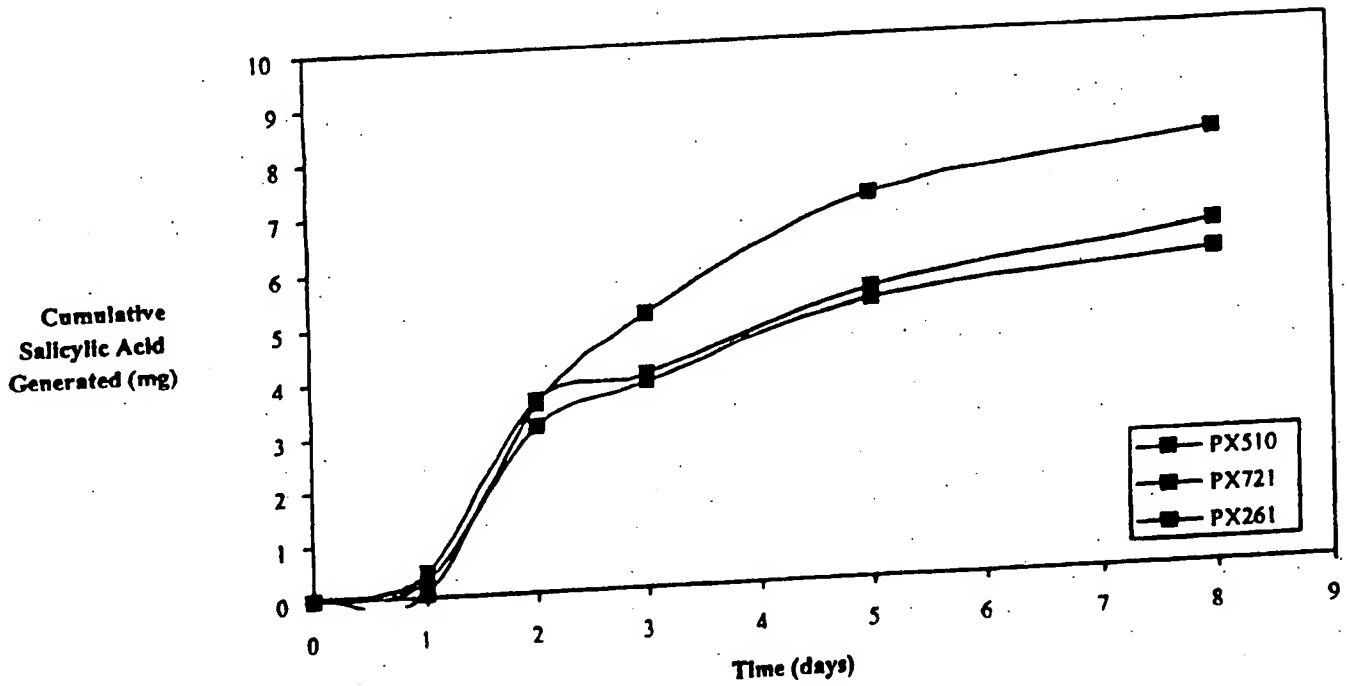

Cumulative Salicylic Acid Generated (mg)
10
9
8
7
6
5
4
3
2
1
0
0
1
2
3
4
5
6
7
8
9
Time (days)
PX510
PX721
PX261

FIGURE 8B

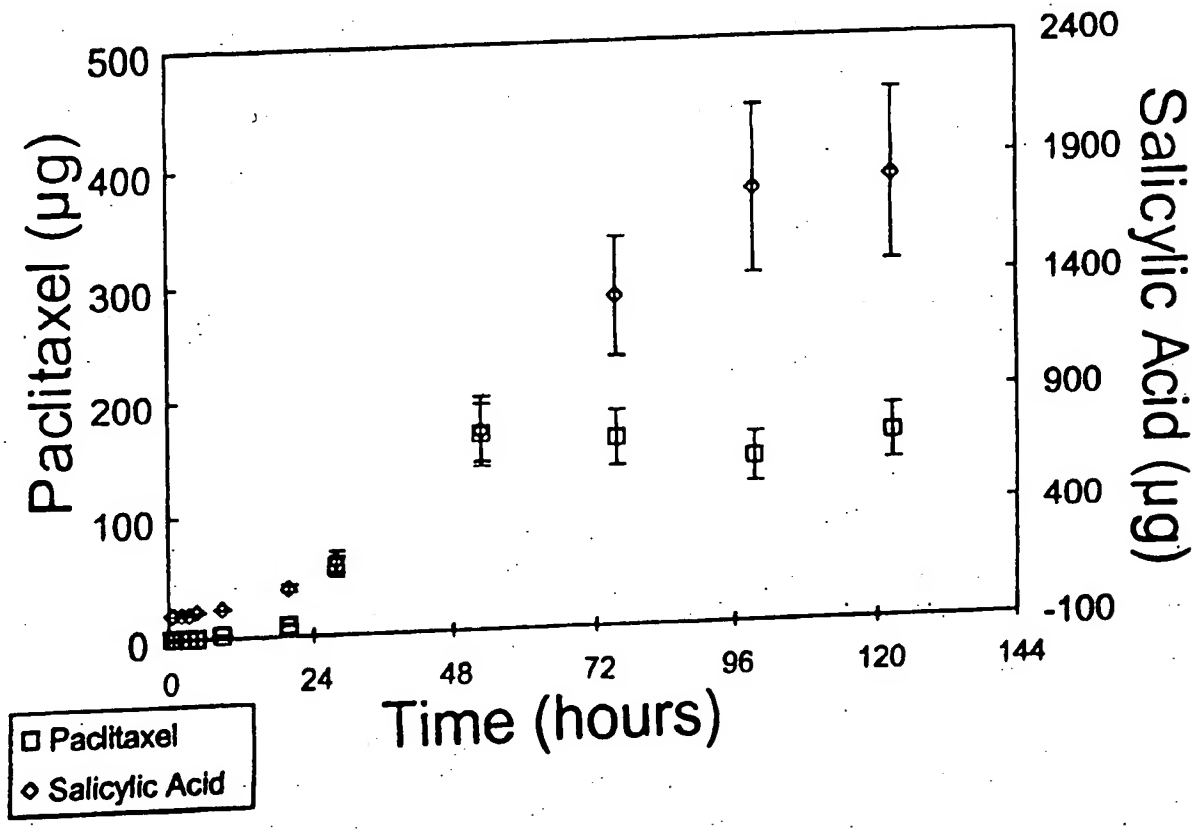

Paclitaxel (µg)
500
400
300
200
100
0
Salicylic Acid (µg)
2400
1900
1400
900
400
-100
0
24
48
72
96
120
144
Time (hours)
Paclitaxel
Salicylic Acid

FIGURE 9A

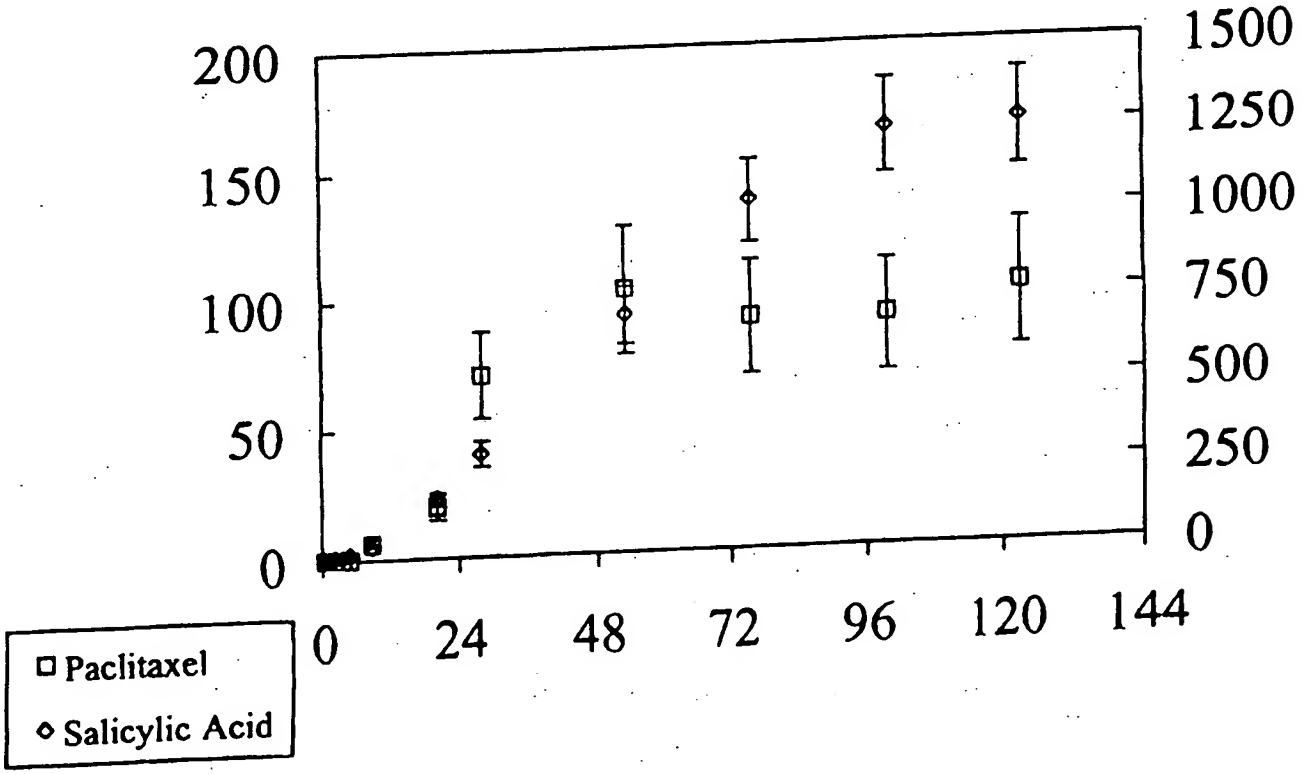

200
150
100
50
0
1500
1250
1000
750
500
250
0
0
24
48
72
96
120
144
Paclitaxel
Salicylic Acid

FIGURE 9B

Property	Formulation			
	PX510	PX721	PX261	PX749
T_g (C)	44	38	29	16
Tensile modulus (MPa)	2.0 (25 C) 5.1 (37 C)			3.0 (25 C)
Yield Strength (MPa)	Not observed			6.0 (25 C)
Ultimate Elongation (%)	1.5 (25 C) 350 (37 C)			500 (25 C)

FIGURE 10

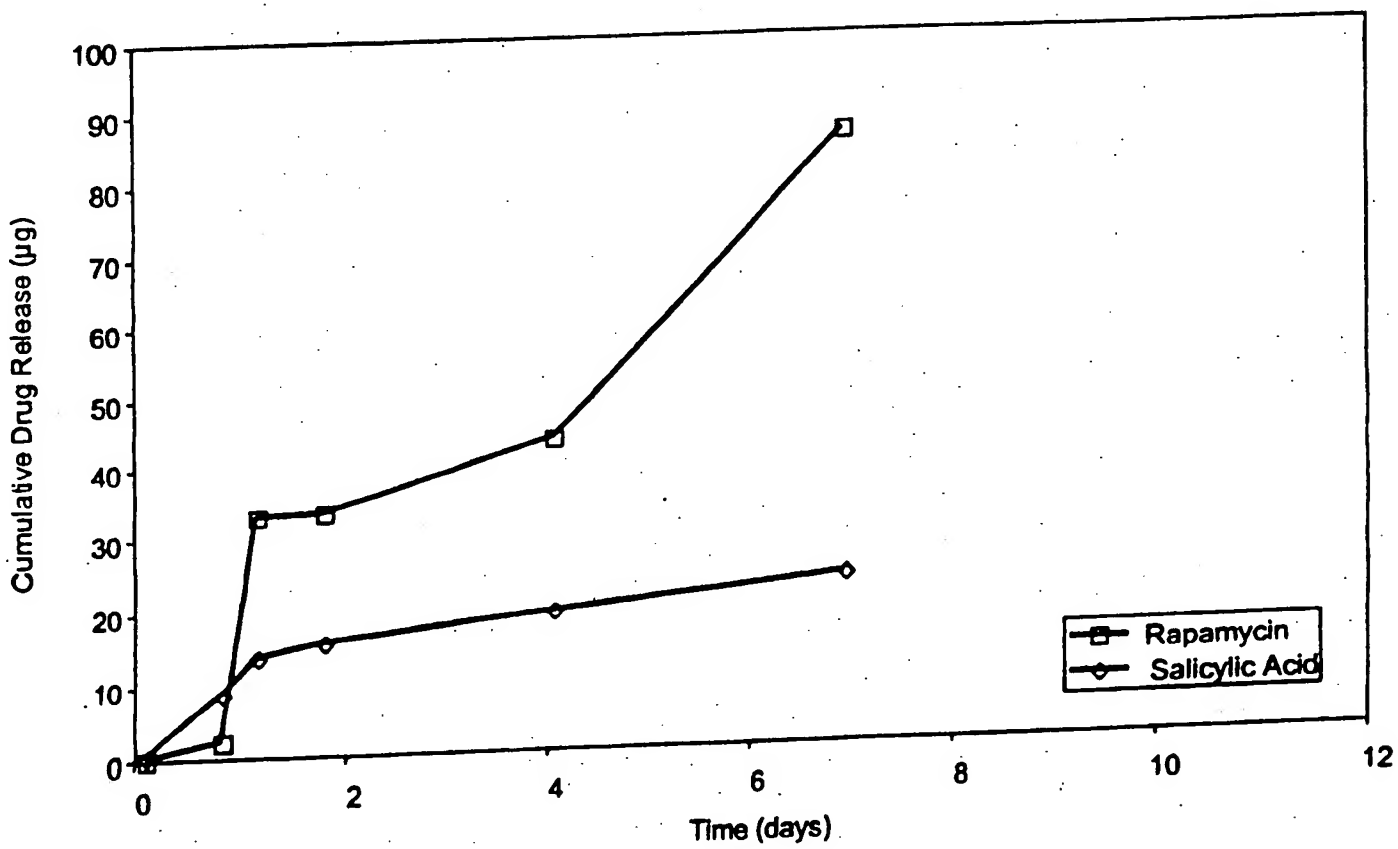

Cumulative Drug Release (µg)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
Time (days)
Rapamycin
Salicylic Acid

FIGURE 11

	E Beam (3 MRad)			γ (25-35 KGys)		
Property	PX510	PX721	PX261	PX510	PX721	PX261
MW	-28%	-39%	-26%	-14%	N/C	N/C
Hardness	-2 units	N/C	-1 unit	N/C	-3 units	-2 units
Flexibility	N/C	N/C	N/C	N/C	N/C	N/C
Adhesion	N/C	N/C	-1 unit	N/C	N/C	N/C

N/C: no change

FIGURE 12

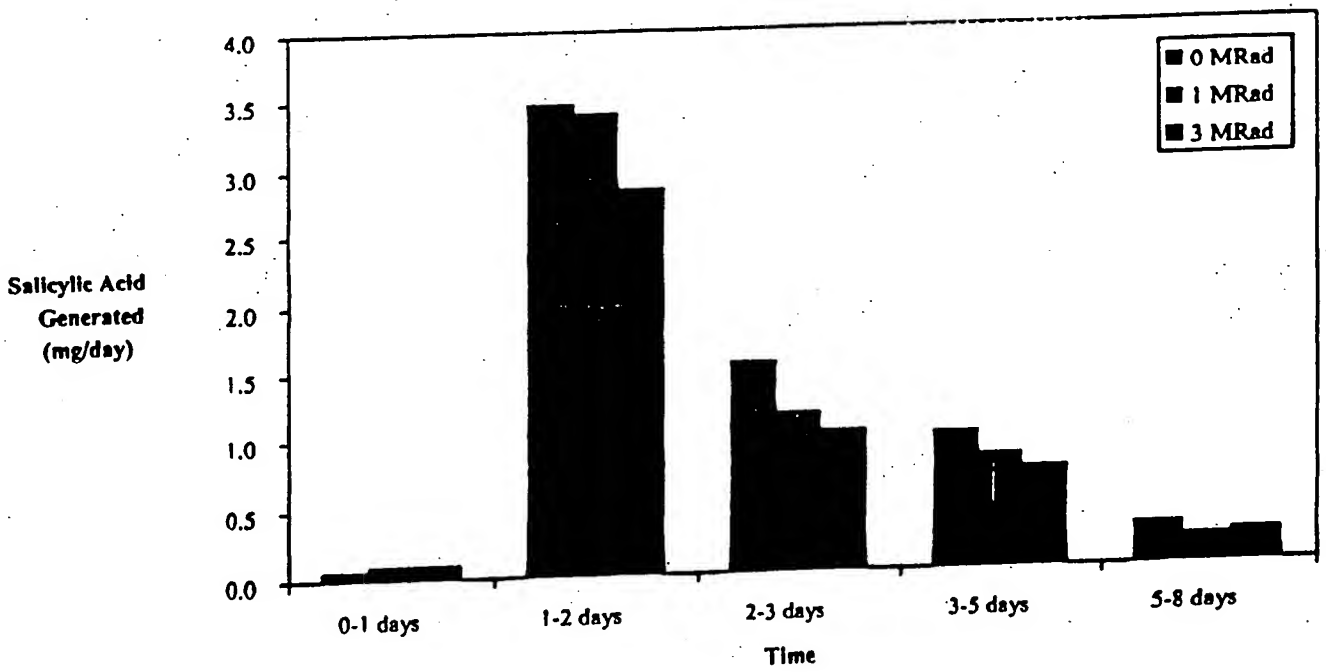

Salicylic Acid Generated (mg/day)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0 MRad
1 MRad
3 MRad
0-1 days
1-2 days
2-3 days
3-5 days
5-8 days
Time

FIGURE 13A

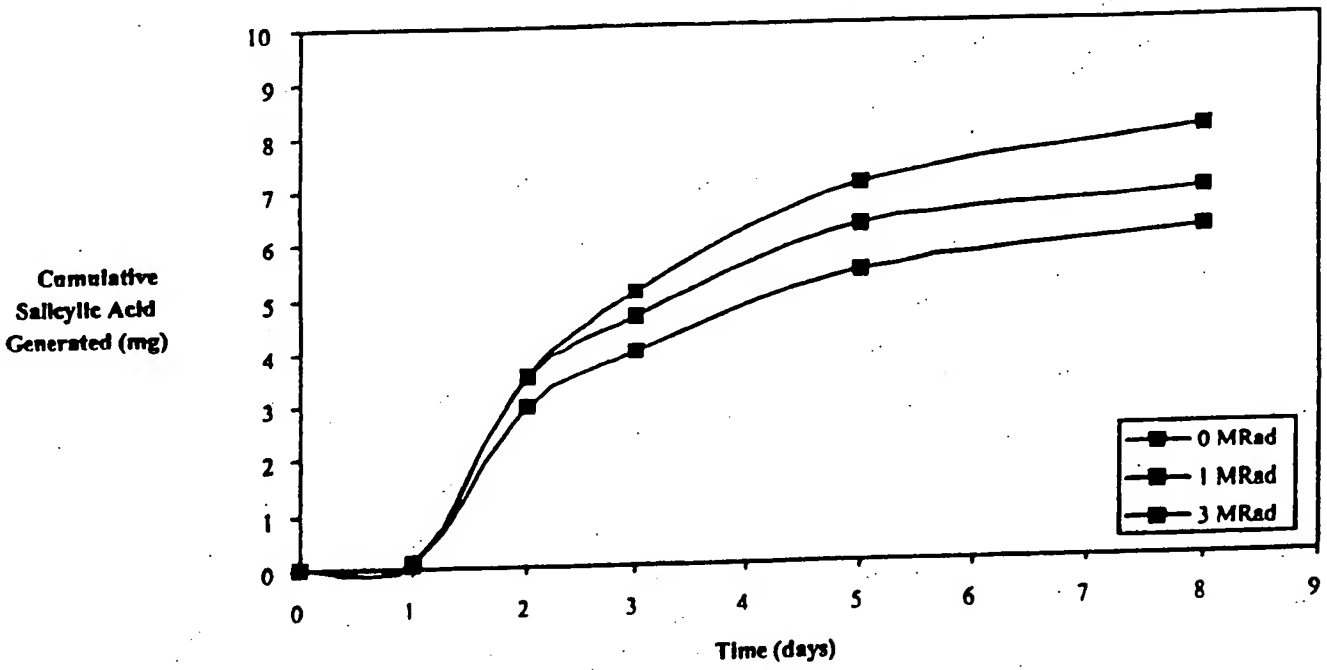

Cumulative Salicylic Acid Generated (mg)
10
9
8
7
6
5
4
3
2
1
0
0
1
2
3
4
5
6
7
8
9
Time (days)
0 MRad
1 MRad
3 MRad

FIGURE 13B

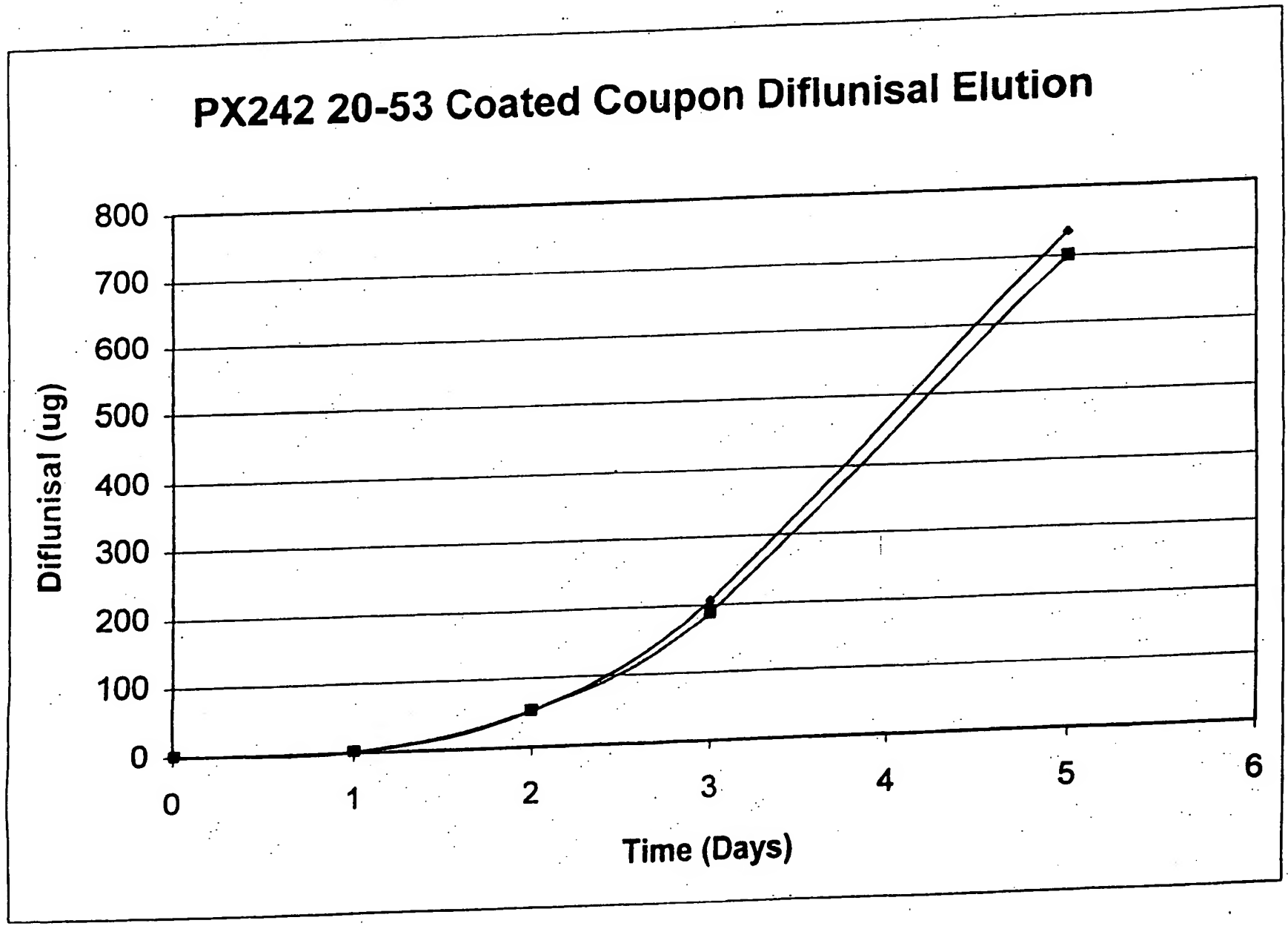

PX242 20-53 Coated Coupon Diflunisal Elution
Diflunisal (ug)
800
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
Time (Days)

FIGURE 14

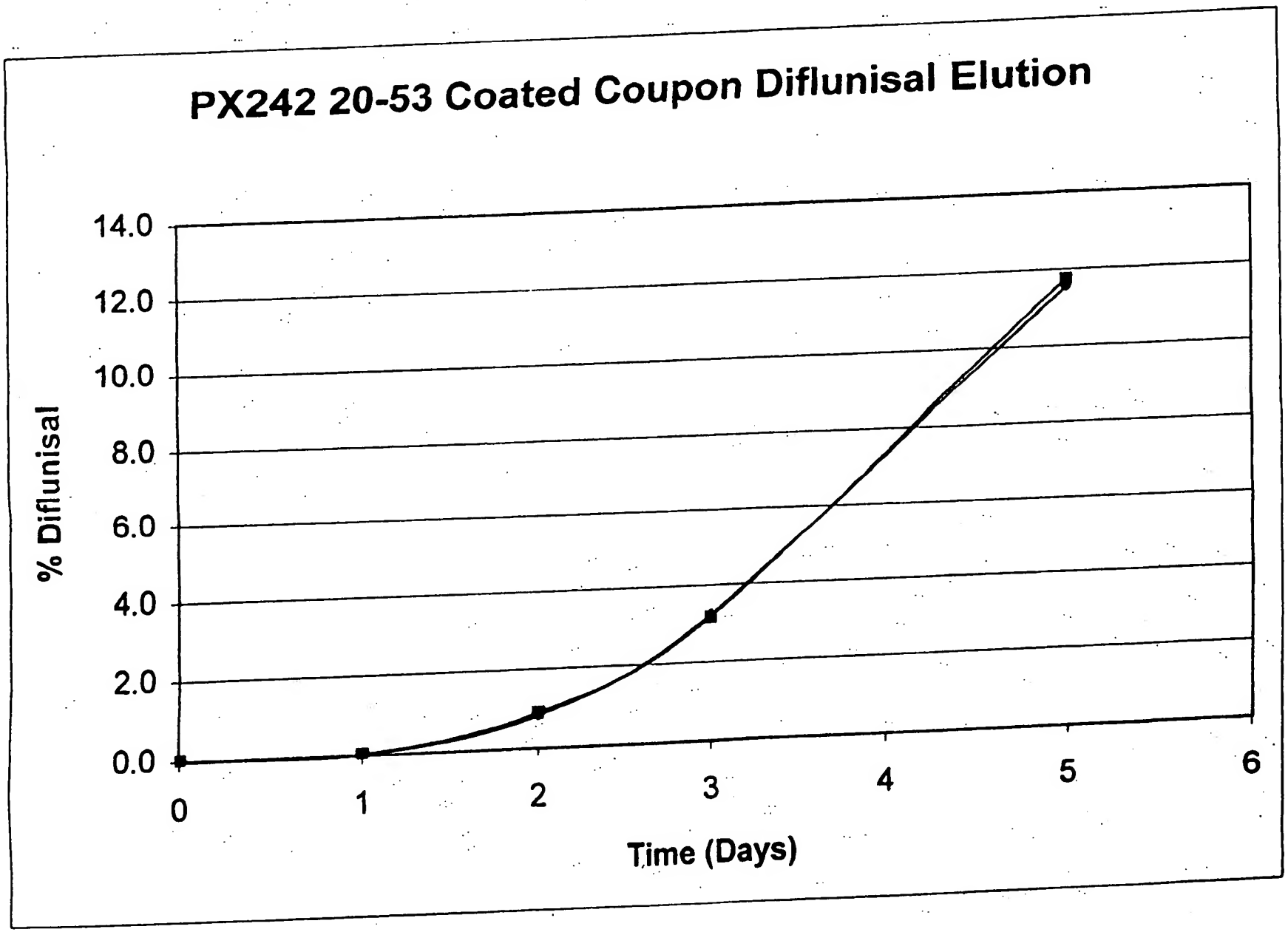

PX242 20-53 Coated Coupon Diflunisal Elution
% Diflunisal
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
0
1
2
3
4
5
6
Time (Days)

FIGURE 15

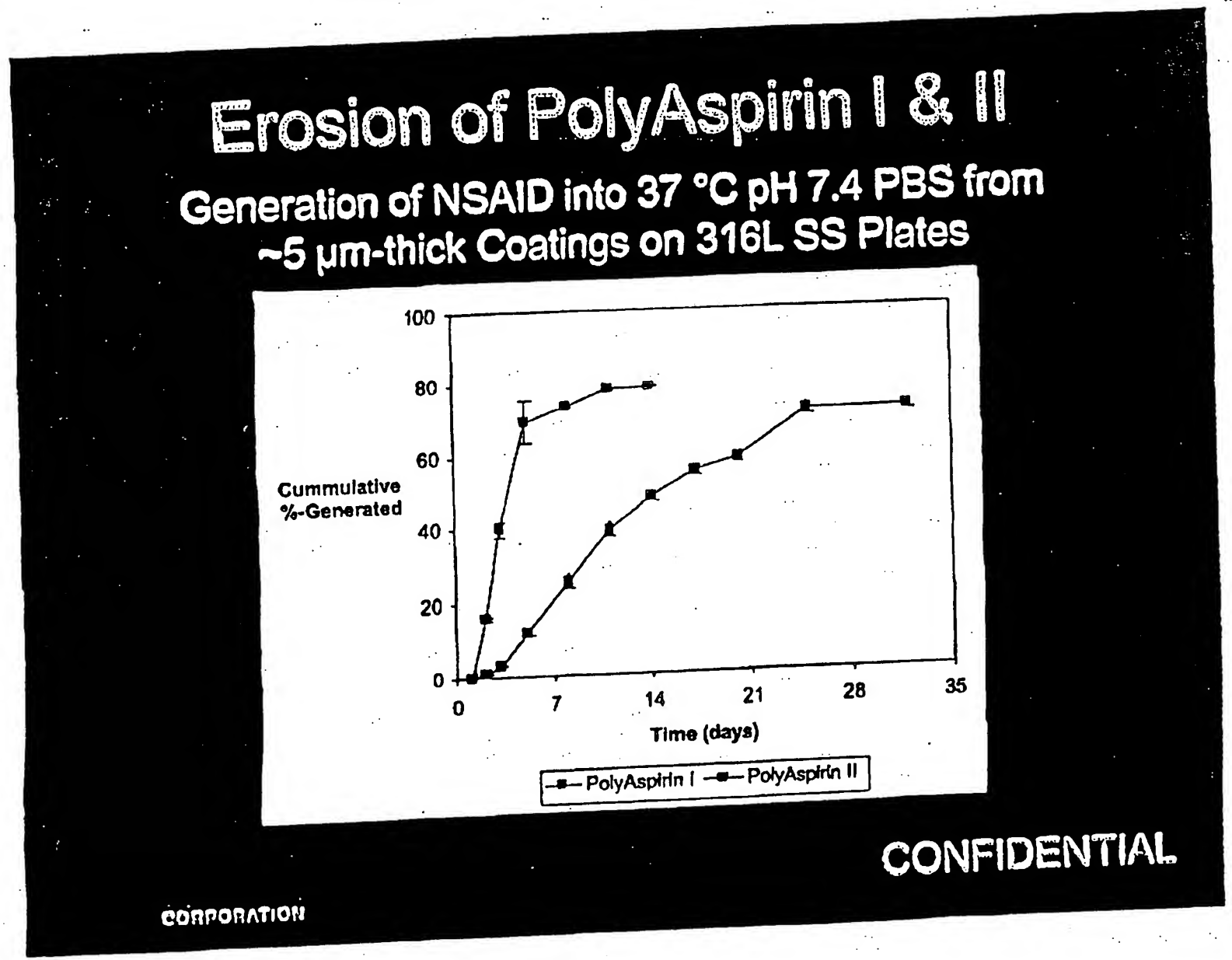

Erosion of PolyAspirin I & II
Generation of NSAID into 37 °C pH 7.4 PBS from ~5 µm-thick Coatings on 316L SS Plates
Cummulative %-Generated
100
80
60
40
20
0
0
7
14
21
28
35
Time (days)
PolyAspirin I
PolyAspirin II
CONFIDENTIAL
CORPORATION

FIGURE 16

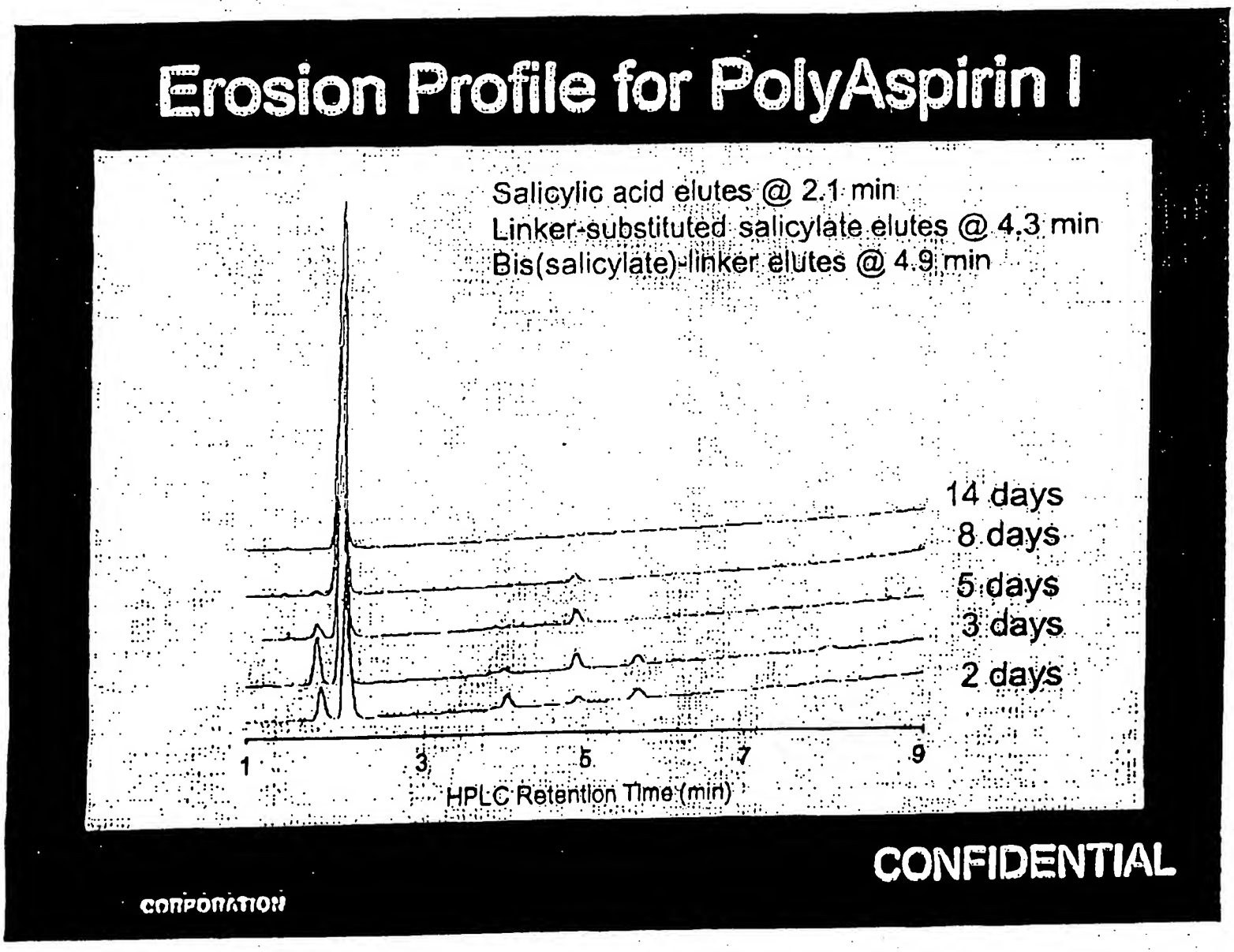

Erosion Profile for PolyAspirin I
Salicylic acid elutes @ 2.1 min
Linker-substituted salicylate elutes @ 4.3 min
Bis(salicylate)-linker elutes @ 4.9 min
14 days
8 days
5 days
3 days
2 days
1
3
5
7
9
HPLC Retention Time (min)
CONFIDENTIAL
CORPORATION

FIGURE 17

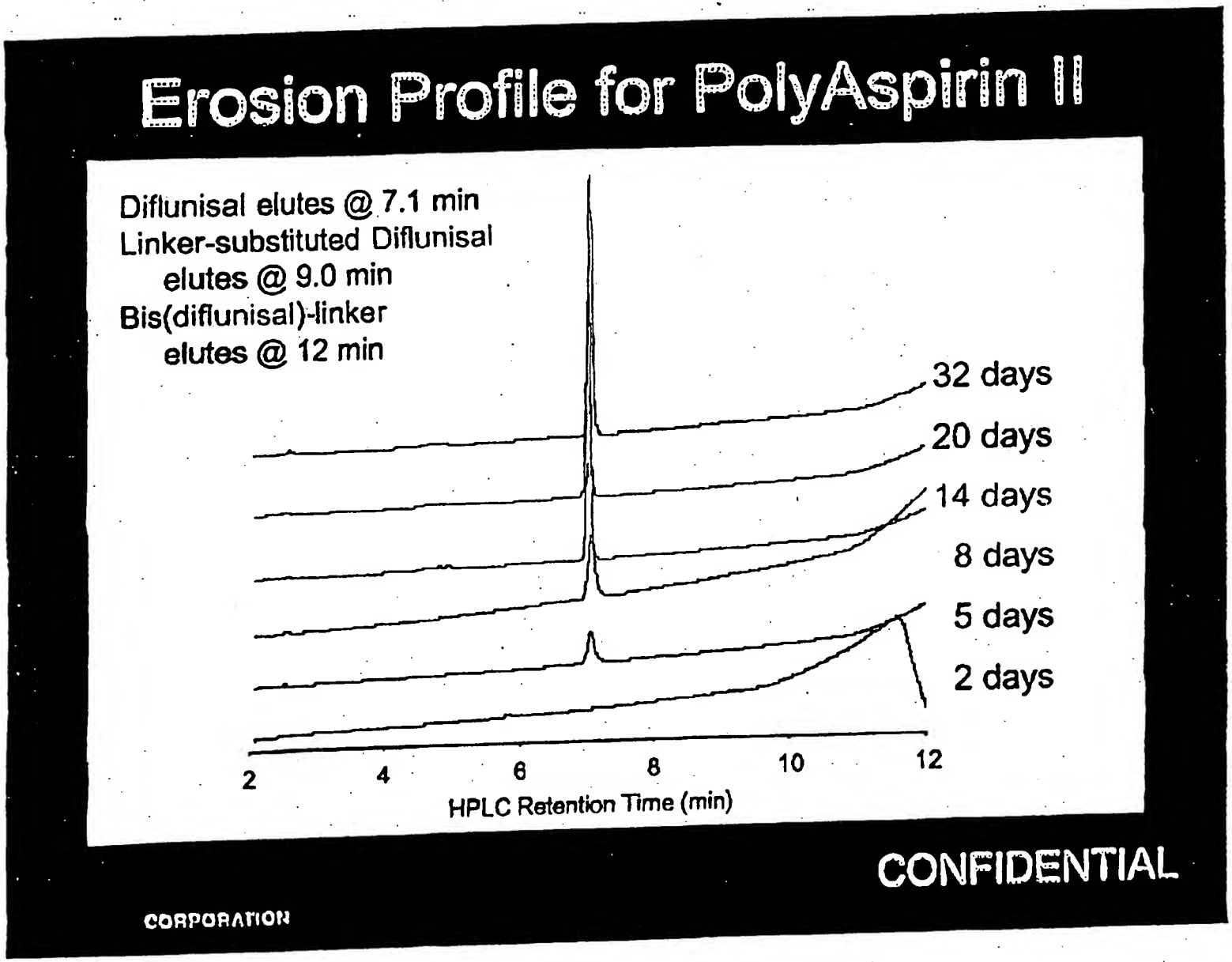

Erosion Profile for PolyAspirin II
Diflunisal elutes @ 7.1 min
Linker-substituted Diflunisal
elutes @ 9.0 min
Bis(diflunisal)-linker
elutes @ 12 min
32 days
20 days
14 days
8 days
5 days
2 days
2
4
6
8
10
12
HPLC Retention Time (min)
CONFIDENTIAL
CORPORATION

FIGURE 18

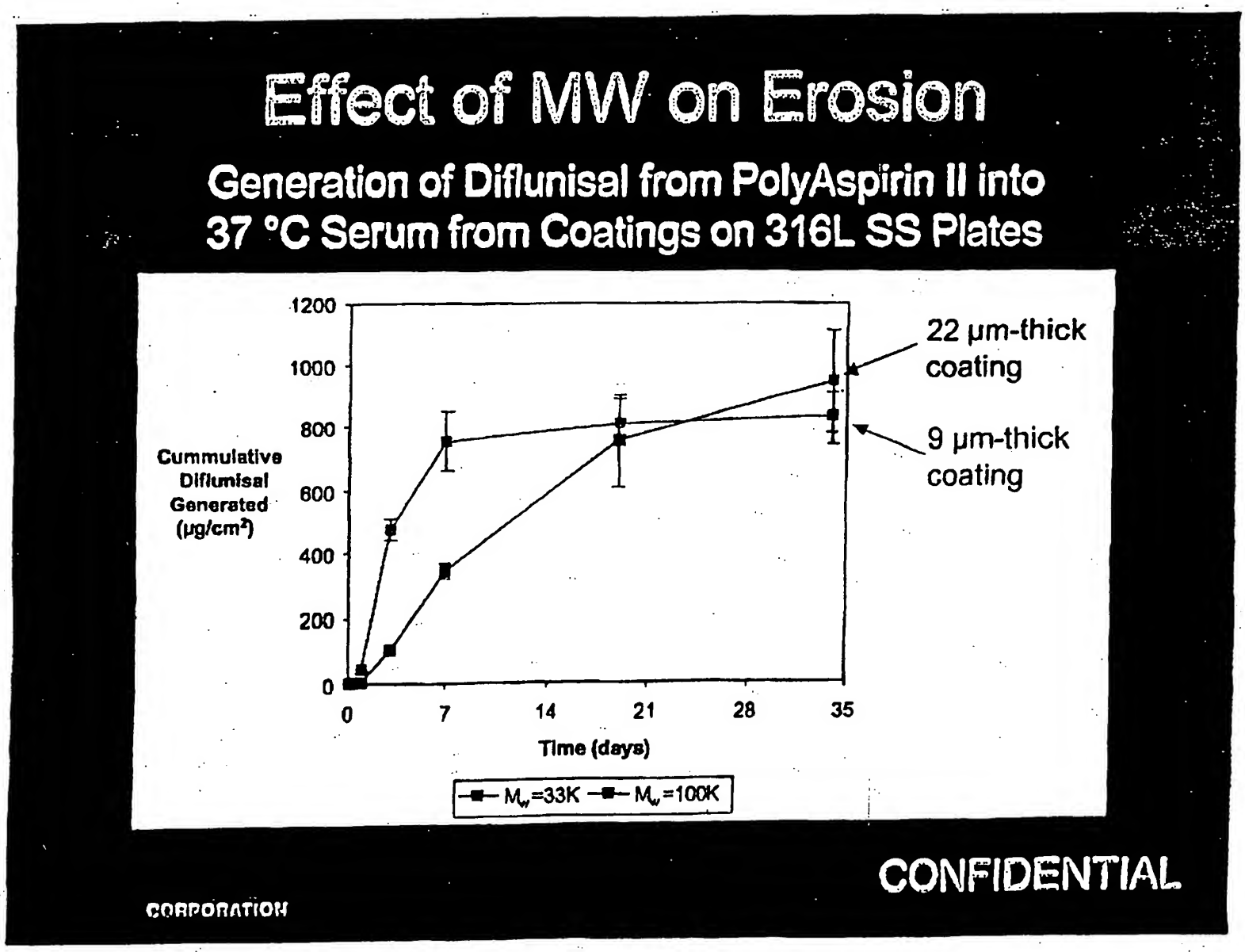

Effect of MW on Erosion
Generation of Diflunisal from PolyAspirin II into 37 °C Serum from Coatings on 316L SS Plates
Cummulative Diflunisal Generated (µg/cm²)
1200
1000
800
600
400
200
0
0
7
14
21
28
35
Time (days)
22 µm-thick coating
9 µm-thick coating
Mw=33K
Mw=100K
CONFIDENTIAL
CORPORATION

FIGURE 19

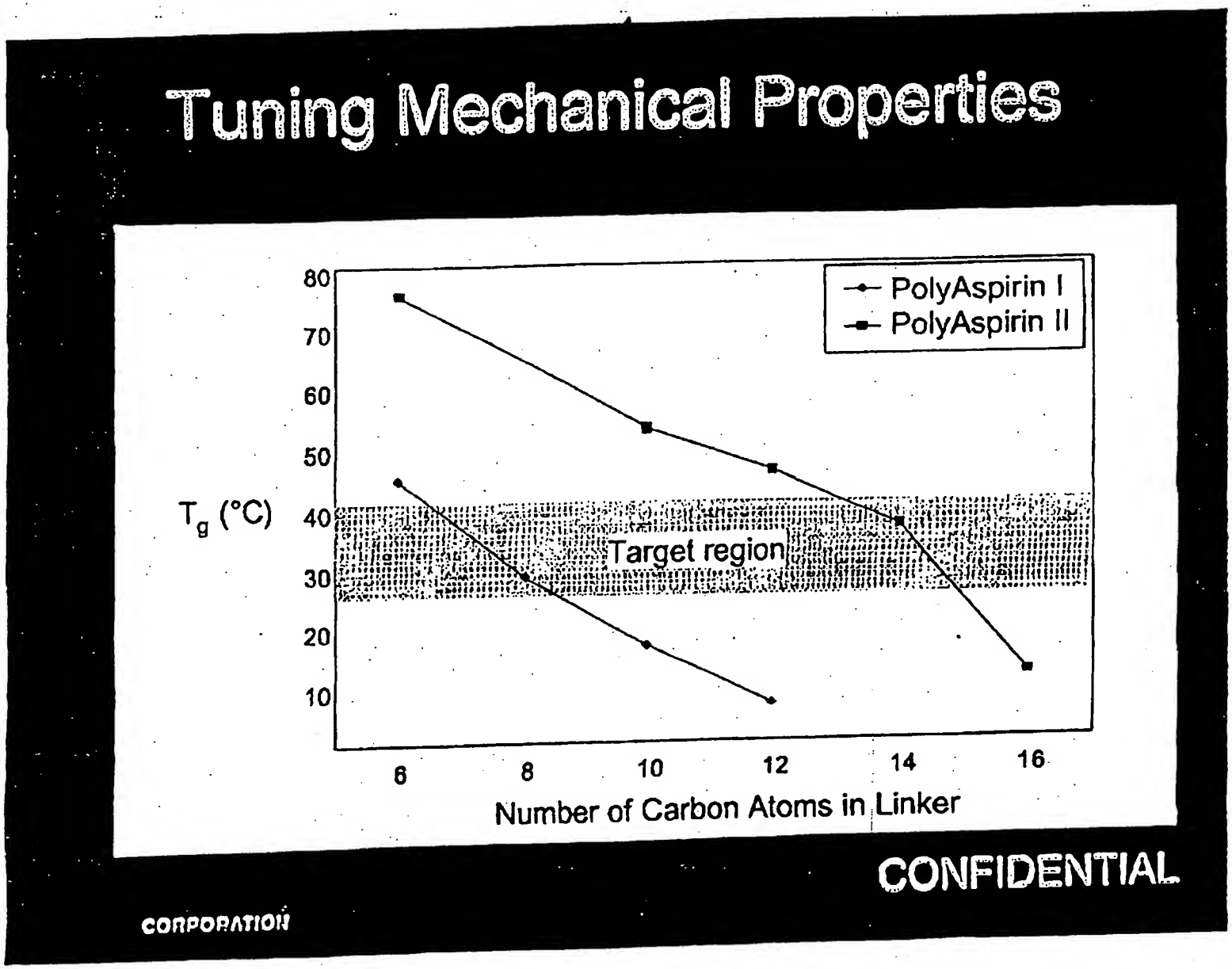

Tuning Mechanical Properties
PolyAspirin I
PolyAspirin II
Target region
T_g (°C)
80
70
60
50
40
30
20
10
6
8
10
12
14
16
Number of Carbon Atoms in Linker
CONFIDENTIAL
CORPORATION

FIGURE 20

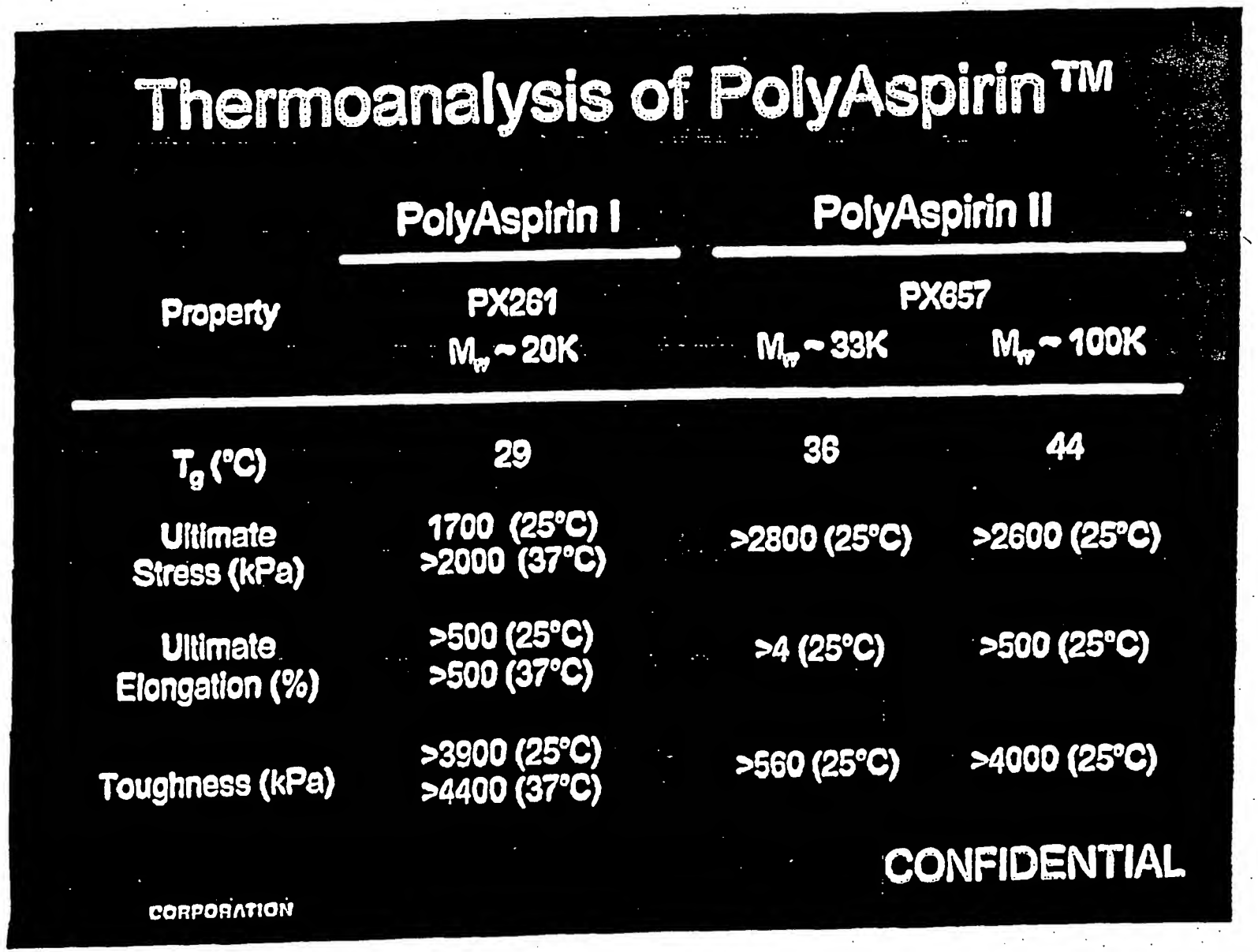

Thermoanalysis of PolyAspirin™
PolyAspirin I
PolyAspirin II
Property
PX261
PX657
M_w ~ 20K
M_w ~ 33K
M_w ~ 100K
T_g (°C)
29
36
44
Ultimate Stress (kPa)
1700 (25°C)
>2000 (37°C)
>2800 (25°C)
>2600 (25°C)
Ultimate Elongation (%)
>500 (25°C)
>500 (37°C)
>4 (25°C)
>500 (25°C)
Toughness (kPa)
>3900 (25°C)
>4400 (37°C)
>560 (25°C)
>4000 (25°C)
CONFIDENTIAL
CORPORATION

FIGURE 21

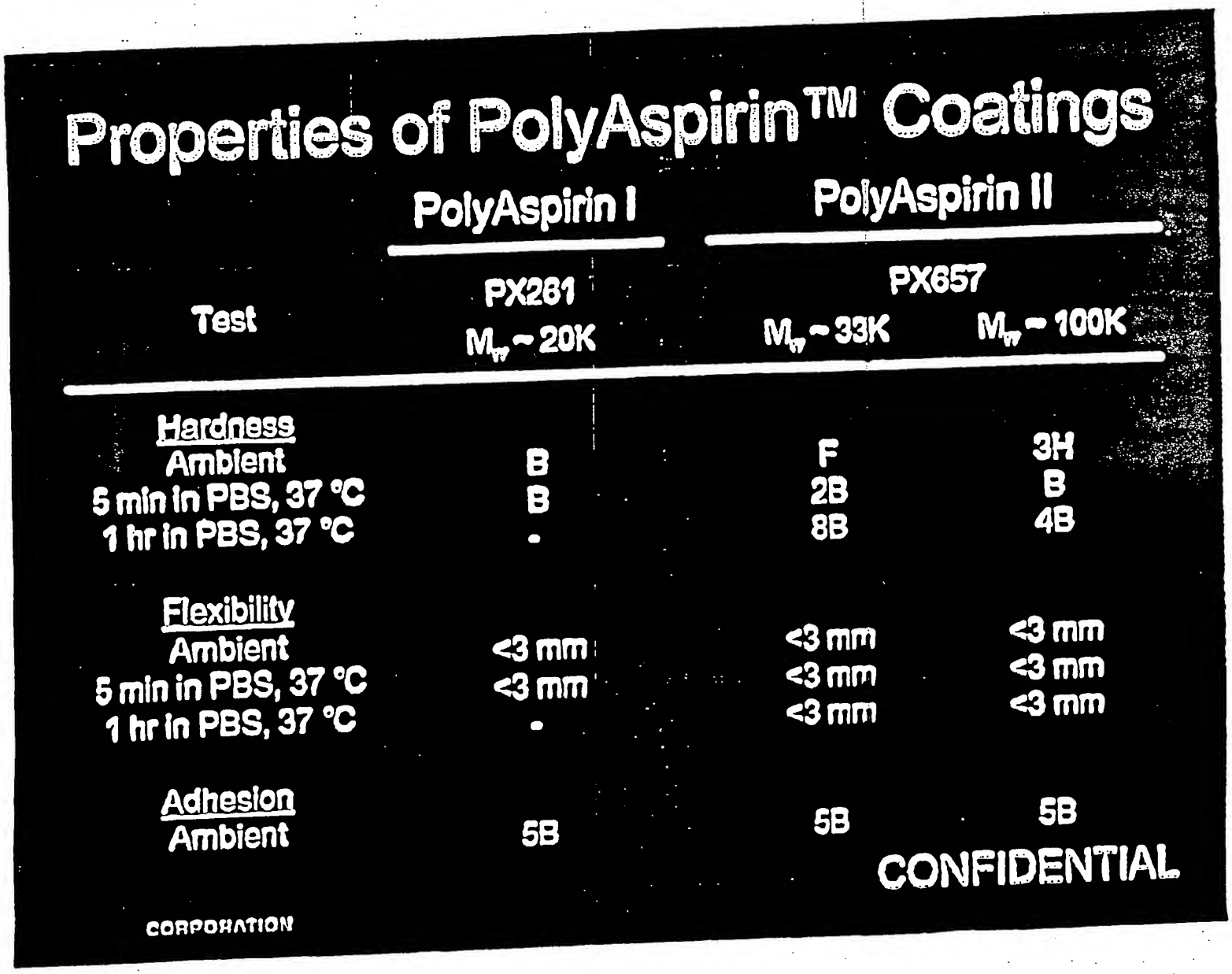

Properties of PolyAspirin™ Coatings
PolyAspirin I
PolyAspirin II
Test
PX261
M_w ~ 20K
PX657
M_w ~ 33K
M_w ~ 100K
Hardness
Ambient
B
F
3H
5 min in PBS, 37 °C
B
2B
B
1 hr in PBS, 37 °C
-
8B
4B
Flexibility
Ambient
<3 mm
<3 mm
<3 mm
5 min in PBS, 37 °C
<3 mm
<3 mm
<3 mm
1 hr in PBS, 37 °C
-
<3 mm
<3 mm
Adhesion
Ambient
5B
5B
5B
CONFIDENTIAL
CORPORATION

FIGURE 22

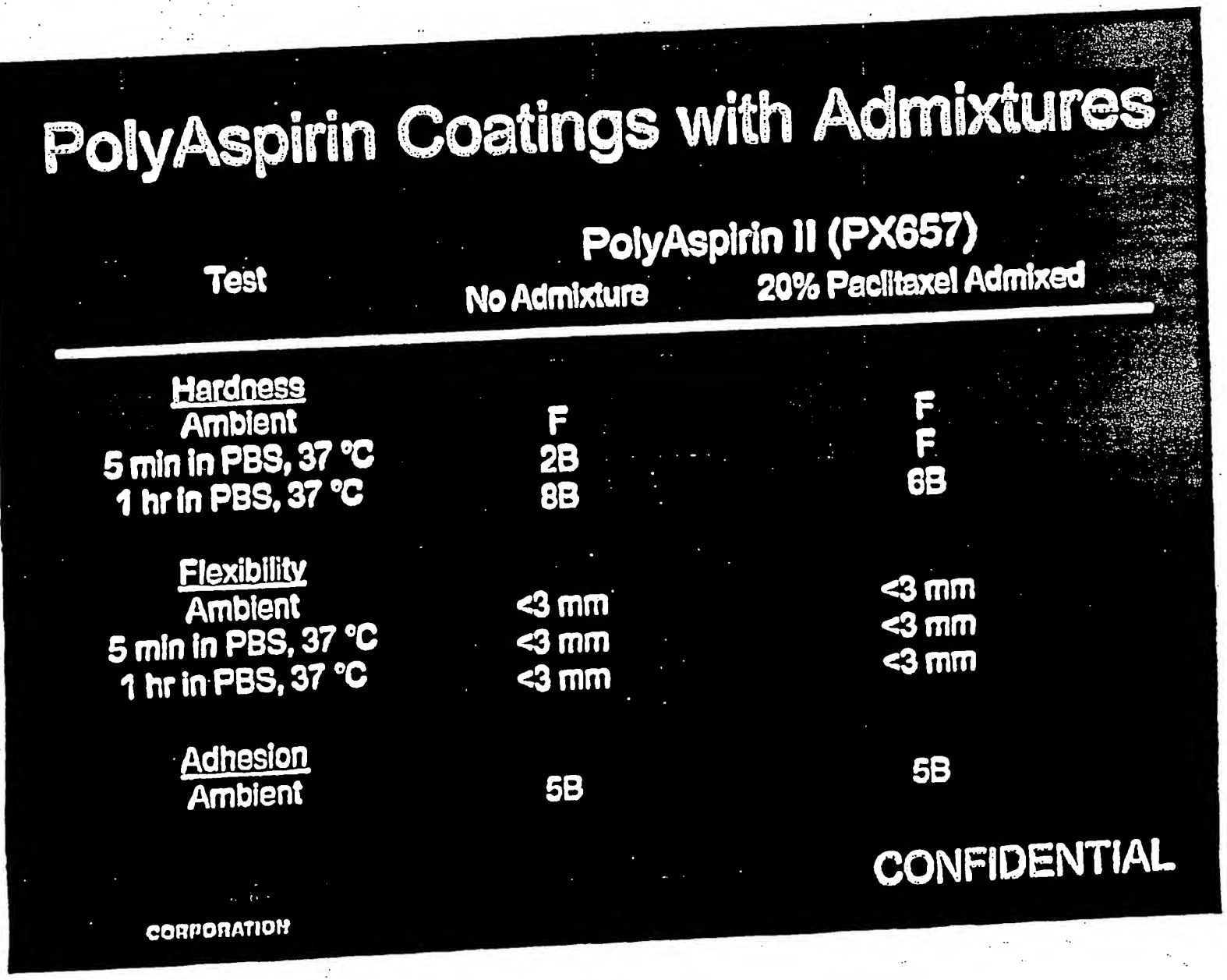
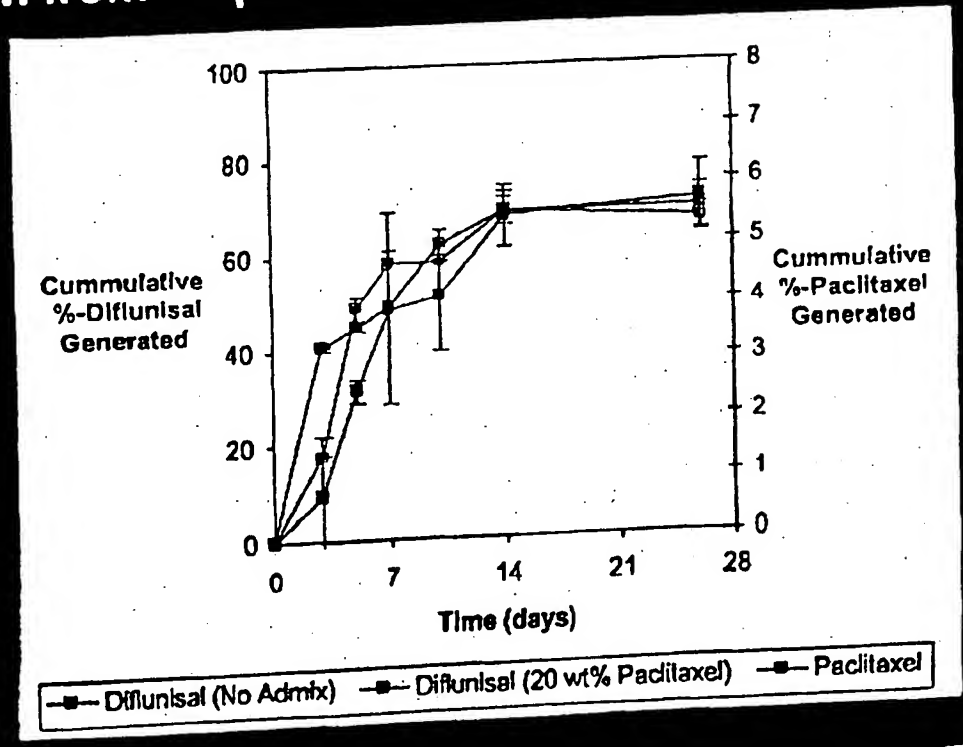

PolyAspirin Coatings with Admixtures
Test
PolyAspirin II (PX657)
No Admixture
20% Paclitaxel Admixed
Hardness
Ambient
F
F
5 min in PBS, 37 °C
2B
F
1 hr in PBS, 37 °C
8B
6B
Flexibility
Ambient
<3 mm
<3 mm
5 min in PBS, 37 °C
<3 mm
<3 mm
1 hr in PBS, 37 °C
<3 mm
<3 mm
Adhesion
Ambient
5B
5B
CONFIDENTIAL
CORPORATION

FIGURE 23

Erosion of PolyAspirin I & II

Diflunisal Generation & Paclitaxel Release into 37 °C Serum from ~5 µm-thick Coatings on 316L SS Plates



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CORPORATION

FIGURE 24

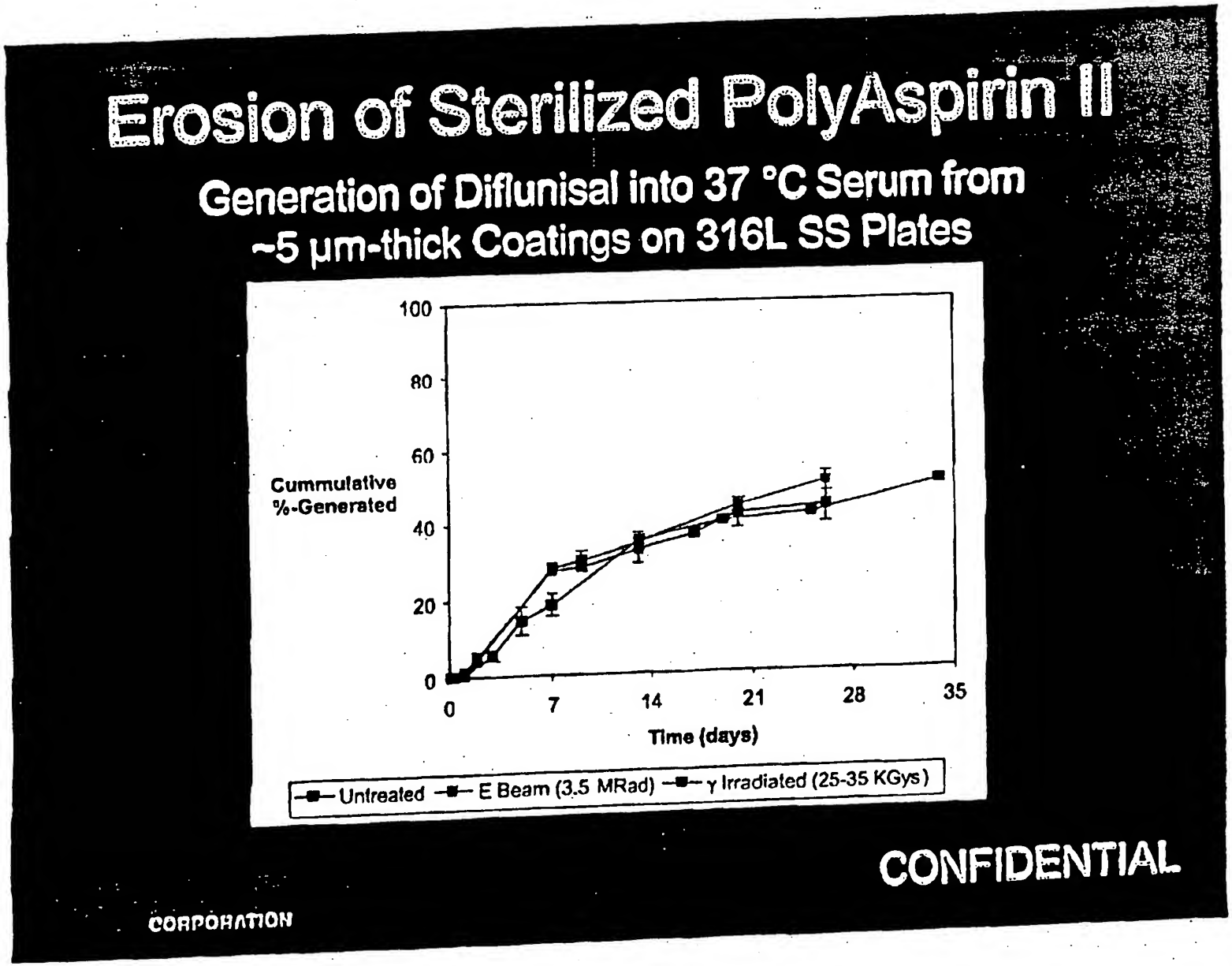

Erosion of Sterilized PolyAspirin II
Generation of Diflunisal into 37 °C Serum from
~5 µm-thick Coatings on 316L SS Plates
Cummulative
%-Generated
100
80
60
40
20
0
0
7
14
21
28
35
Time (days)
Untreated
E Beam (3.5 MRad)
γ Irradiated (25-35 KGys)
CONFIDENTIAL
CORPORATION

FIGURE 25

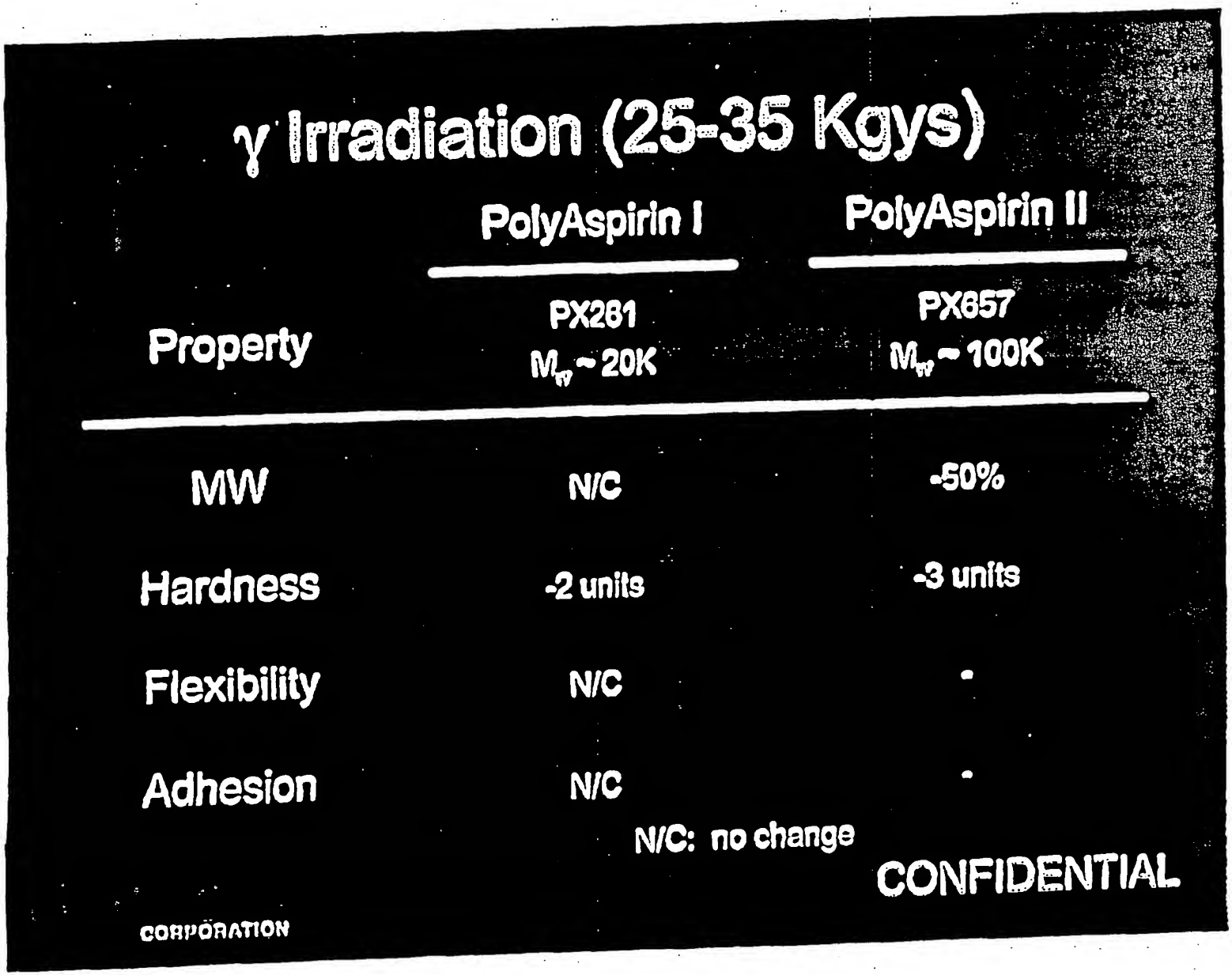

γ Irradiation (25-35 Kgys)
PolyAspirin I
PolyAspirin II
Property
PX261
M_w ~ 20K
PX657
M_w ~ 100K
MW
N/C
-50%
Hardness
-2 units
-3 units
Flexibility
N/C
-
Adhesion
N/C
-
N/C: no change
CONFIDENTIAL
CORPORATION

FIGURE 26

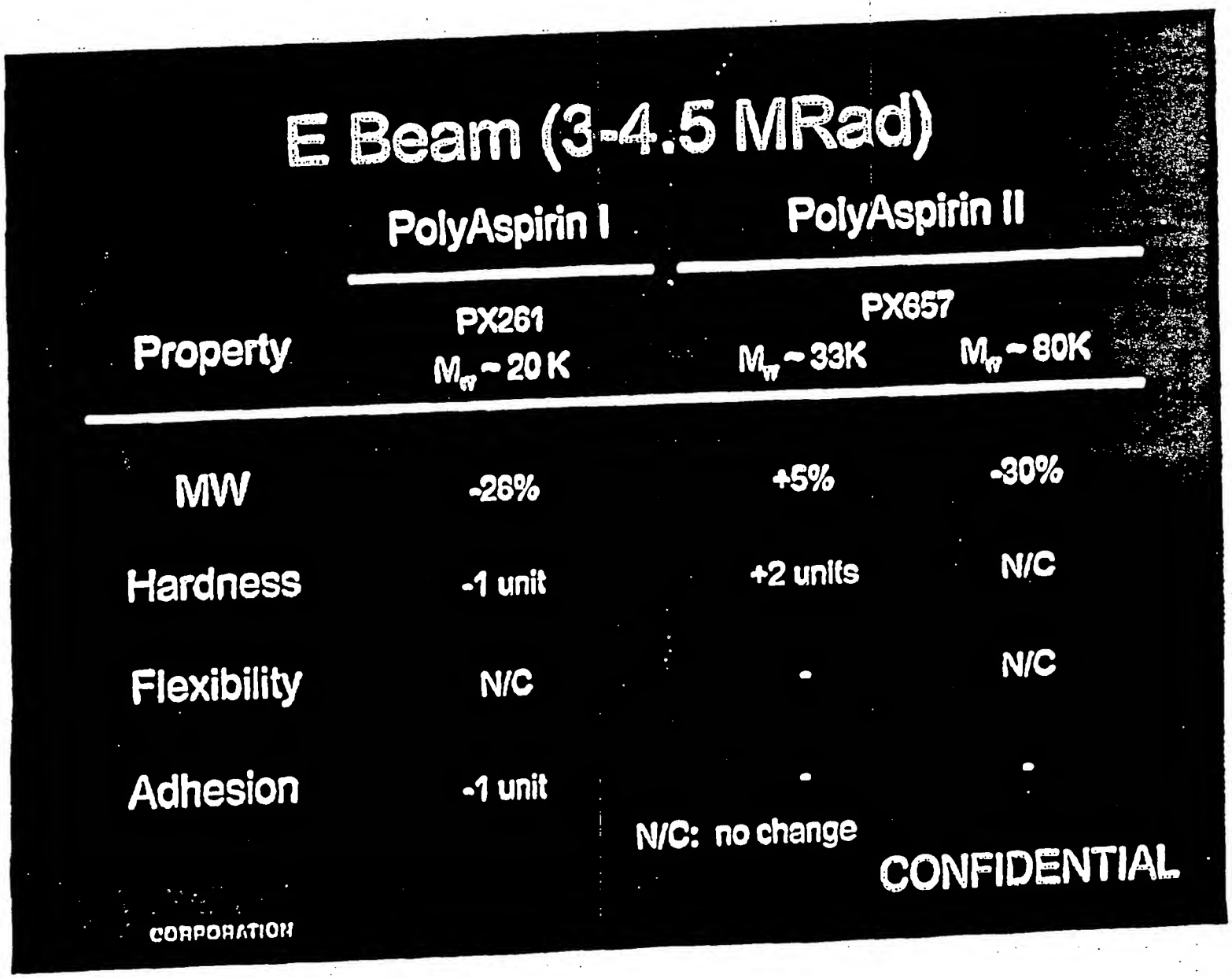

E Beam (3-4.5 MRad)
PolyAspirin I
PolyAspirin II
Property
PX261
M_w ~ 20 K
PX657
M_w ~ 33K
M_w ~ 80K
MW
-26%
+5%
-30%
Hardness
-1 unit
+2 units
N/C
Flexibility
N/C
-
N/C
Adhesion
-1 unit
-
-
N/C: no change
CONFIDENTIAL
CORPORATION

FIGURE 27

Kinetics of NSAID Generation

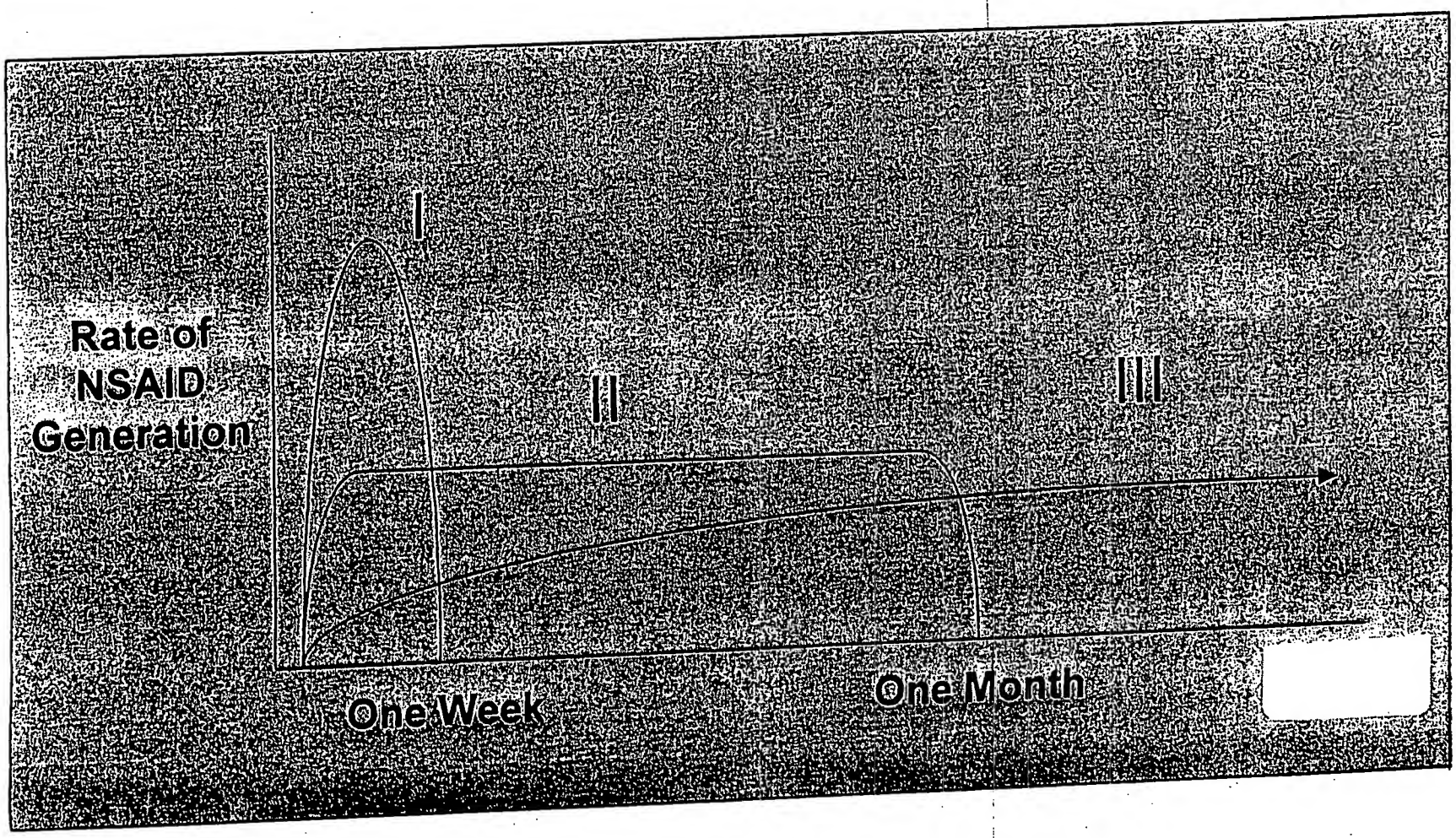


FIGURE 28

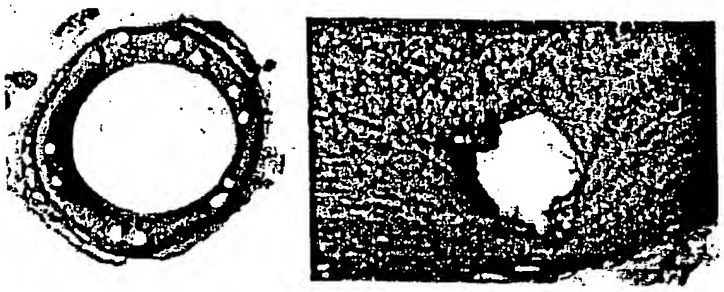


FIGURE 29

FIGURE 30

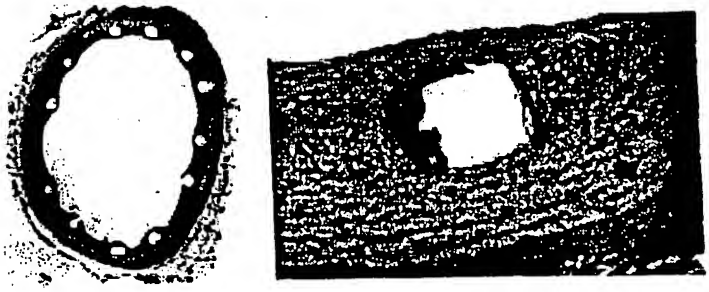


FIGURE 31

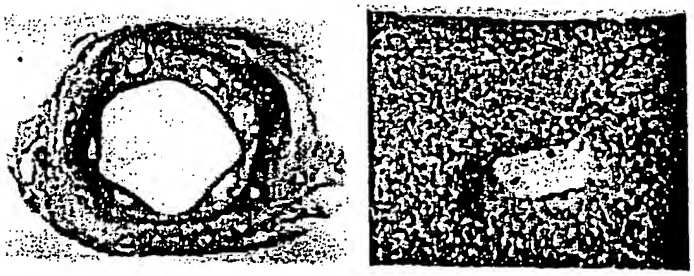


FIGURE 32

FIGURE 33

FIGURE 34

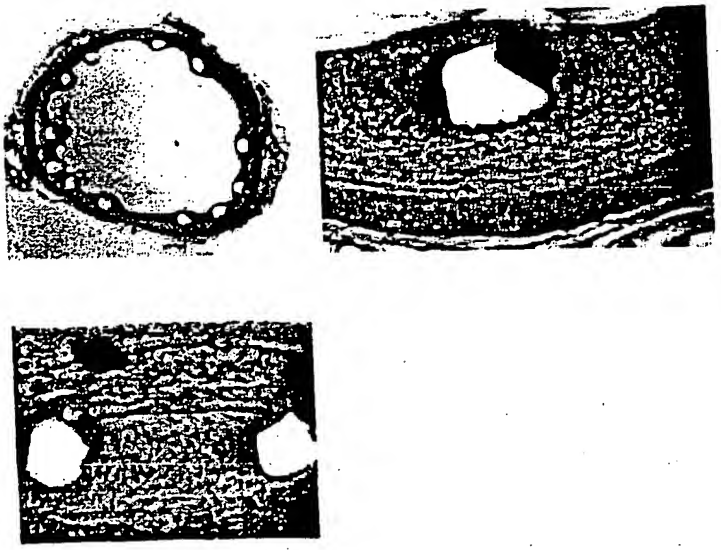


FIGURE 35

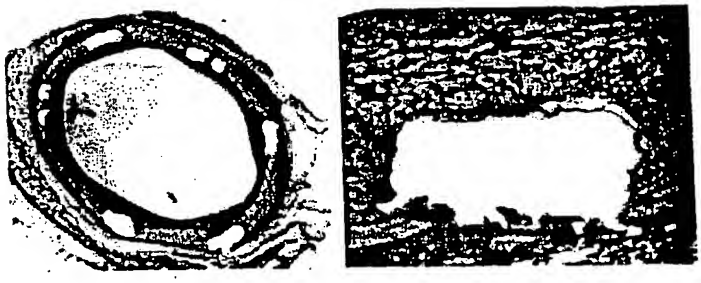


FIGURE 36

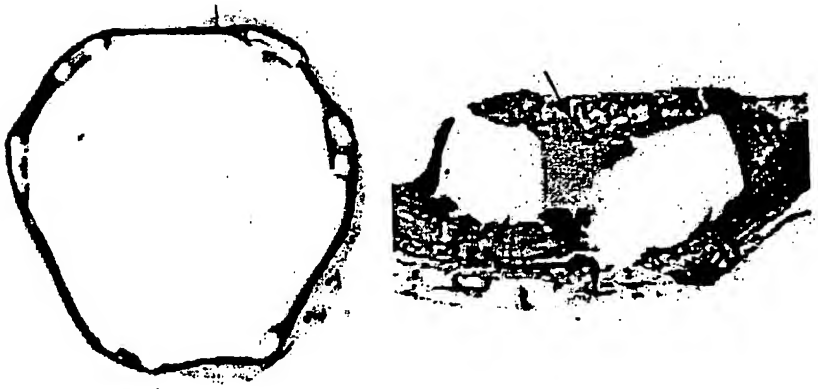


FIGURE 37

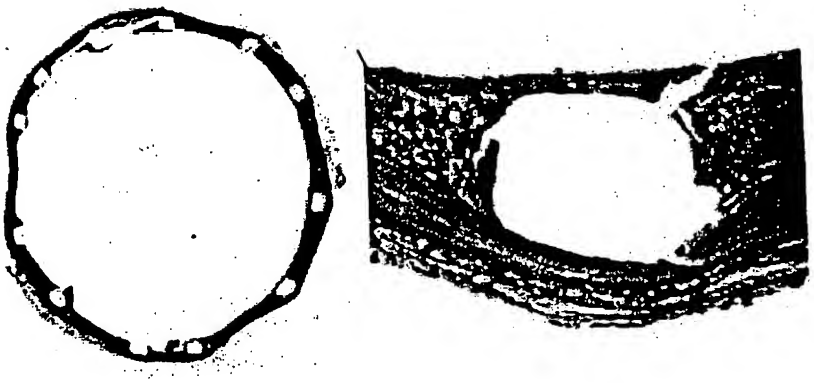
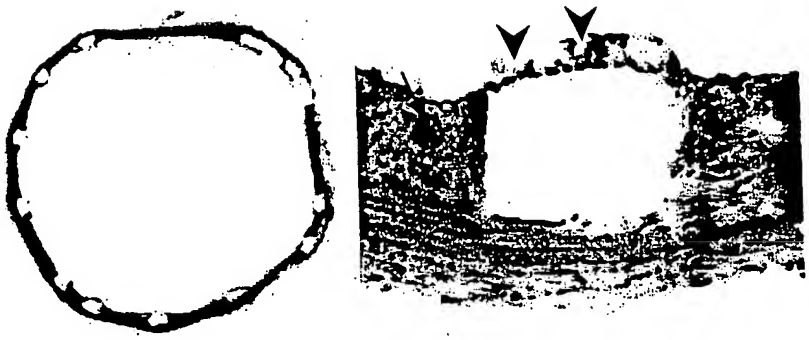


FIGURE 38

FIGURE 39



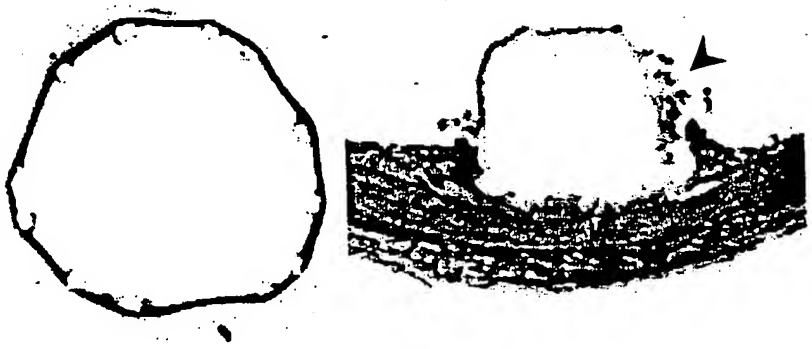


FIGURE 40

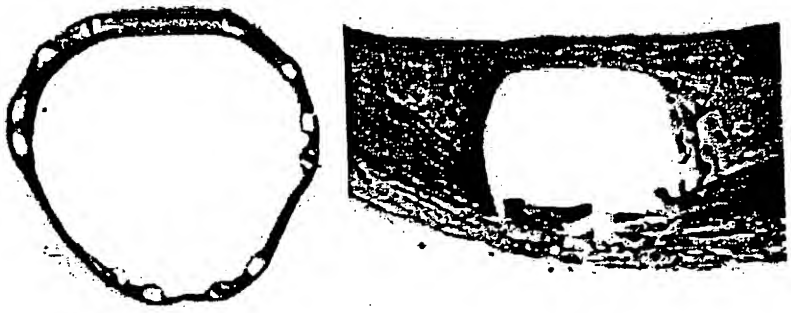


FIGURE 41

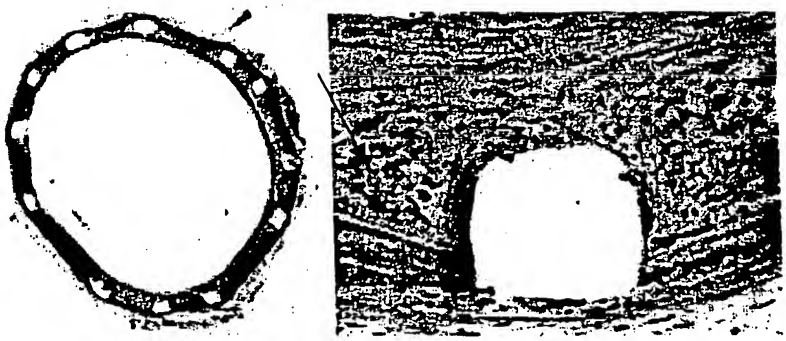


FIGURE 42

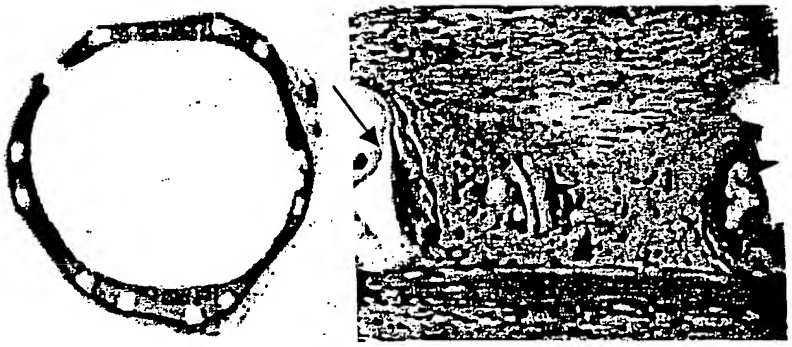


FIGURE 43

uncrimped/unexpanded

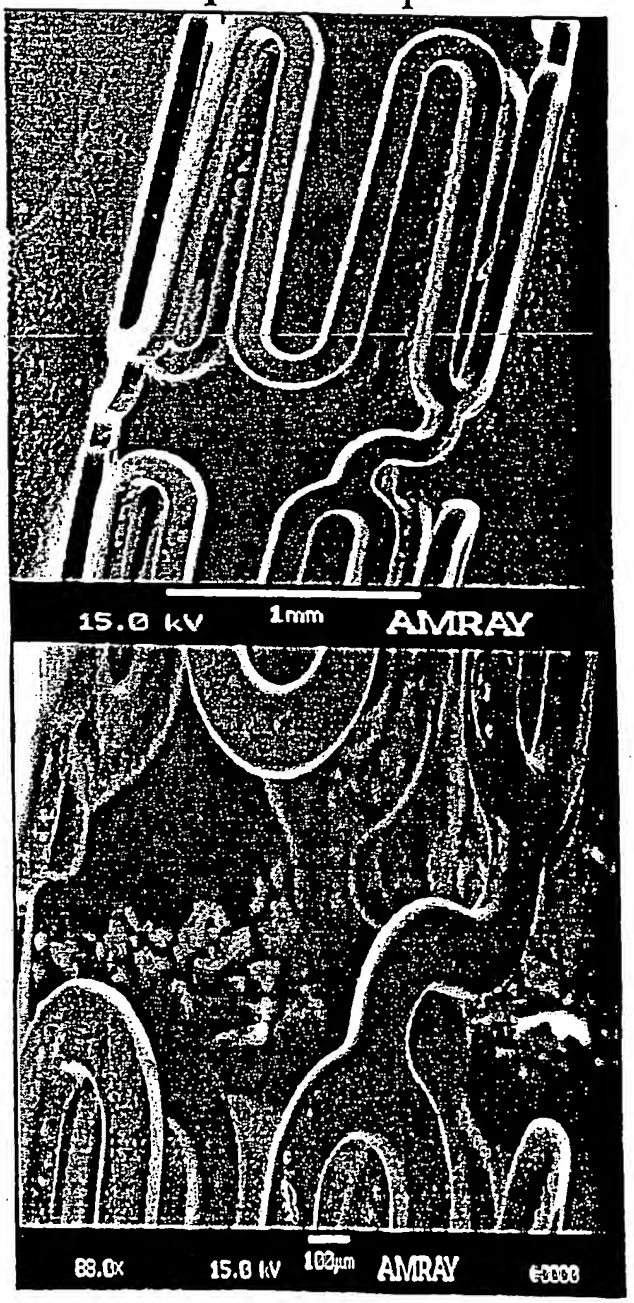


FIG. 44a

FIG. 44b

uncrimped/unexpanded

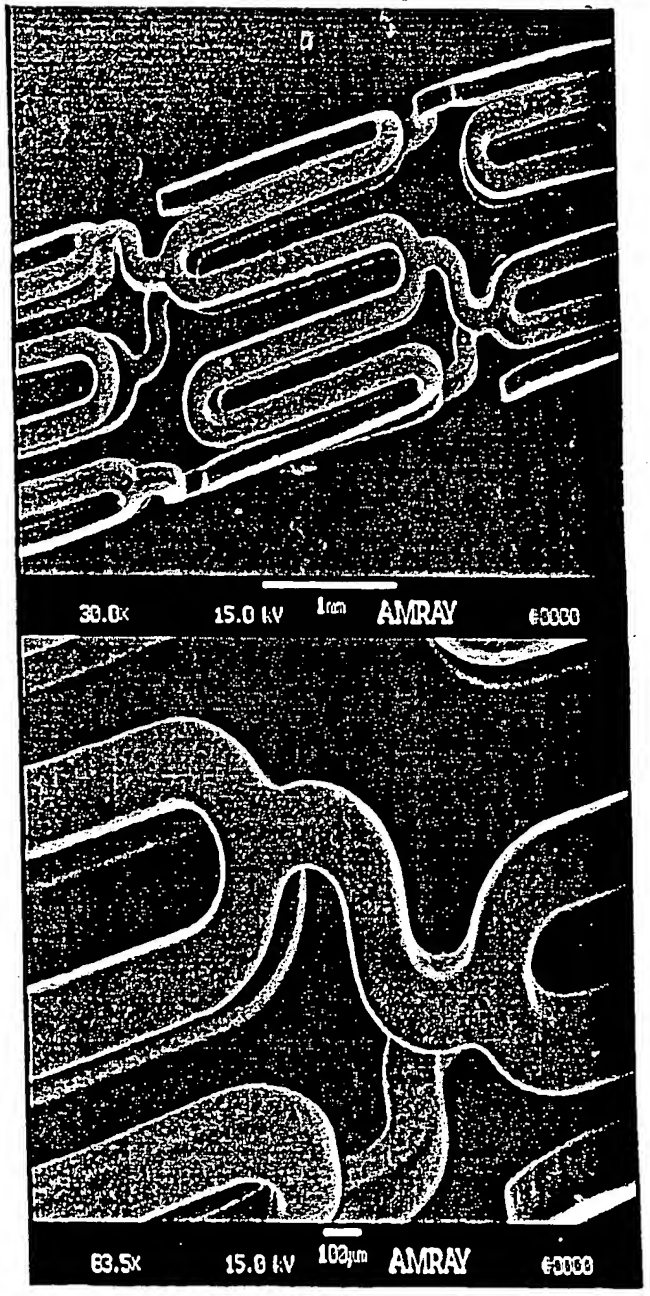


FIG. 45a

FIG. 45b

uncrimped/unexpanded

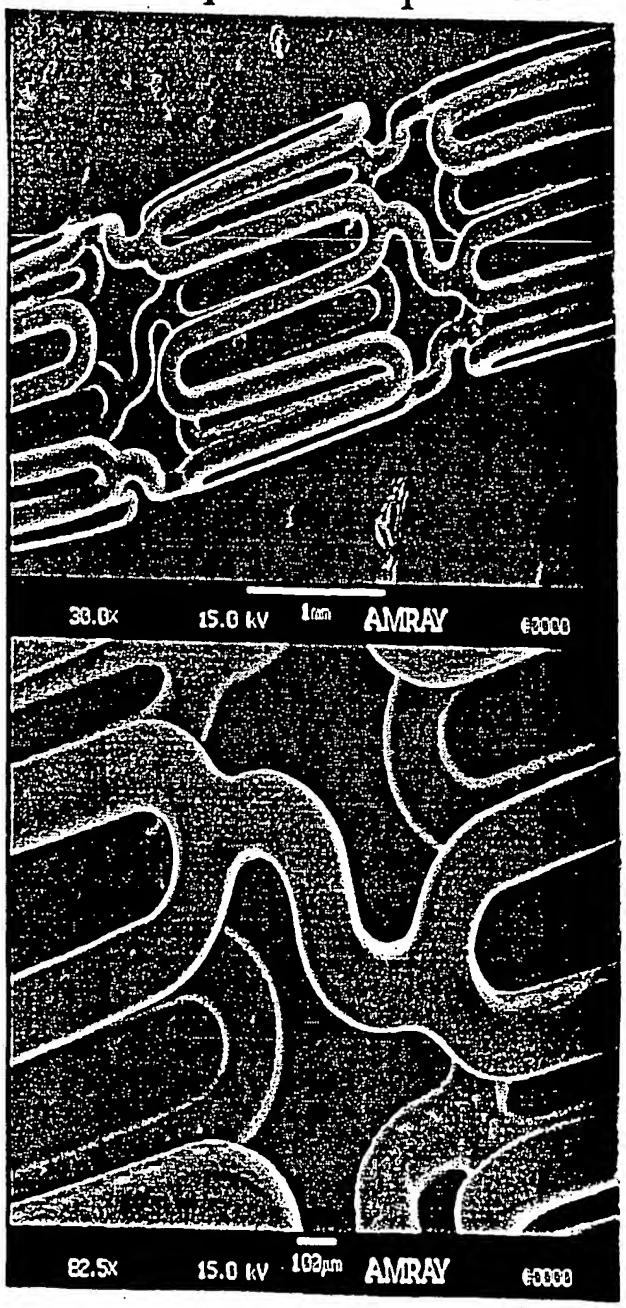


FIG. 46a

FIG. 46b

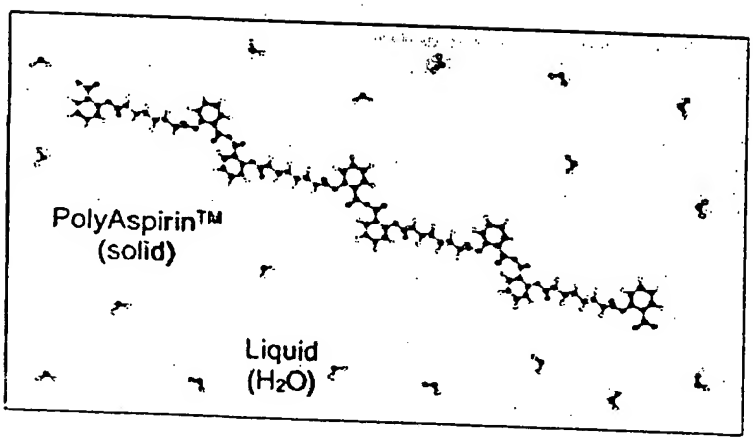


FIGURE 47

FIGURE 48

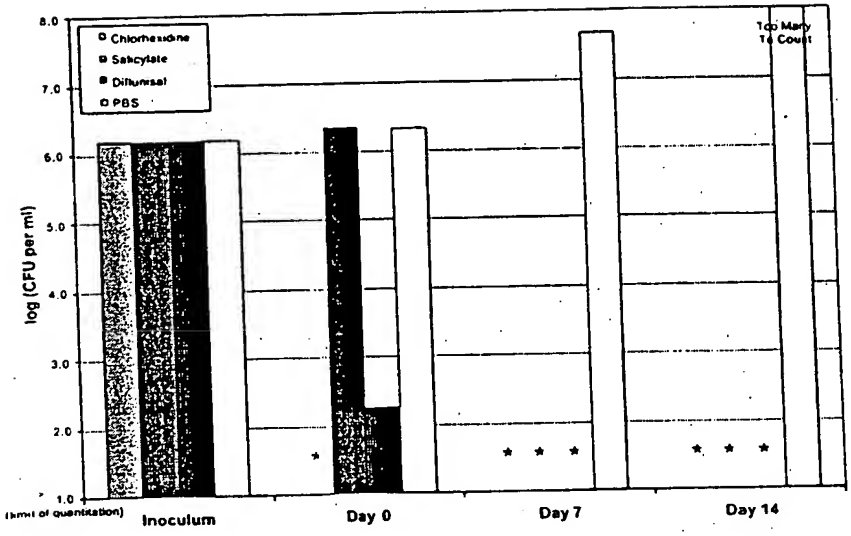

Chlorhexidine
Salicylate
Diflunisal
PBS
log (CFU per ml)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
Too Many To Count
Inoculum
Day 0
Day 7
Day 14

FIGURE 49

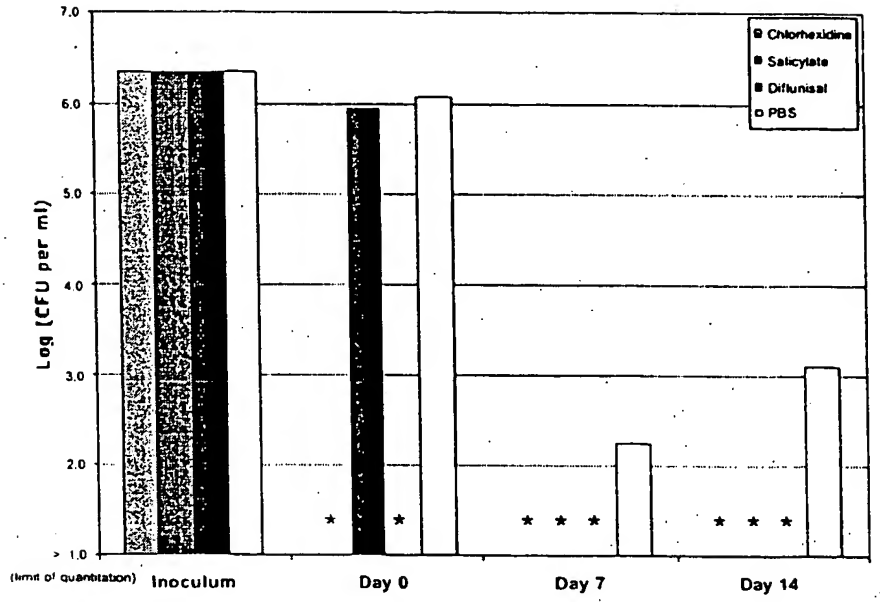

7.0
6.0
5.0
4.0
3.0
2.0
> 1.0
(limit of quantitation)
Log (CFU per ml)
Chlorhexidine
Salicylate
Diflunisal
PBS
Inoculum
Day 0
Day 7
Day 14

FIGURE 50

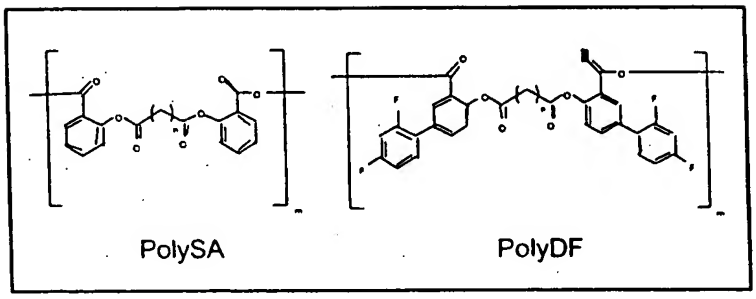


FIGURE 51

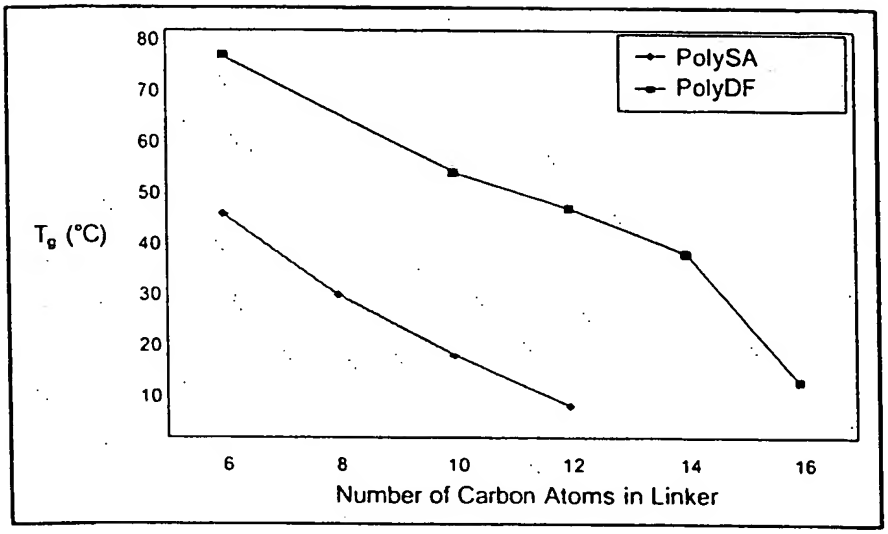

80
70
60
50
40
30
20
10
T_g (°C)
PolySA
PolyDF
6
8
10
12
14
16
Number of Carbon Atoms in Linker

FIGURE 52

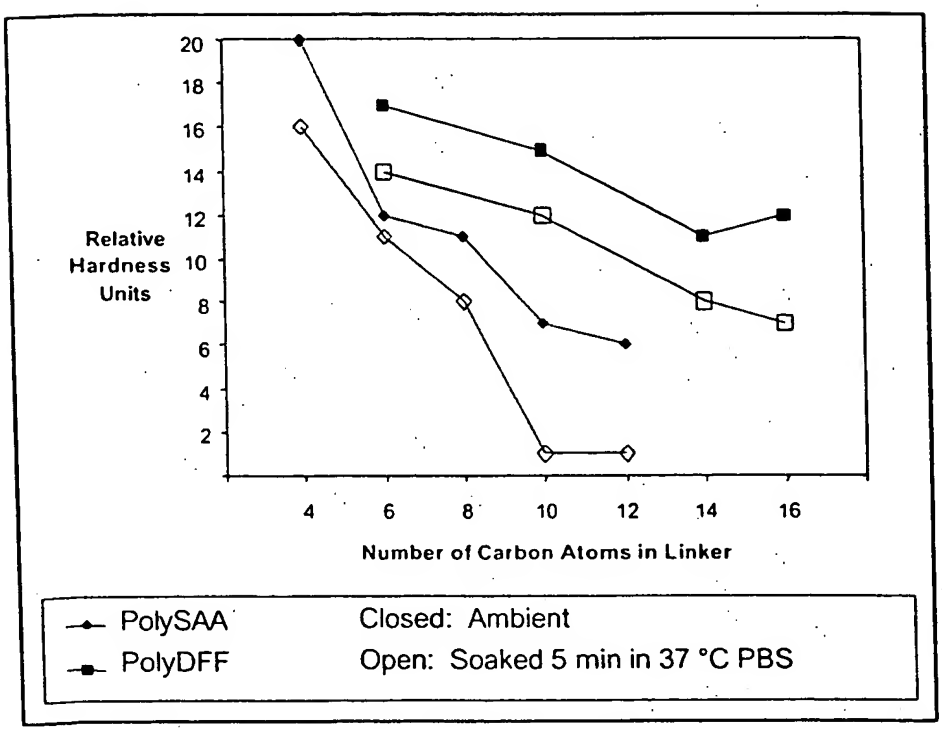

Relative Hardness Units
20
18
16
14
12
10
8
6
4
2
4
6
8
10
12
14
16
Number of Carbon Atoms in Linker
PolySAA
PolyDFF
Closed: Ambient
Open: Soaked 5 min in 37 °C PBS

FIGURE 53

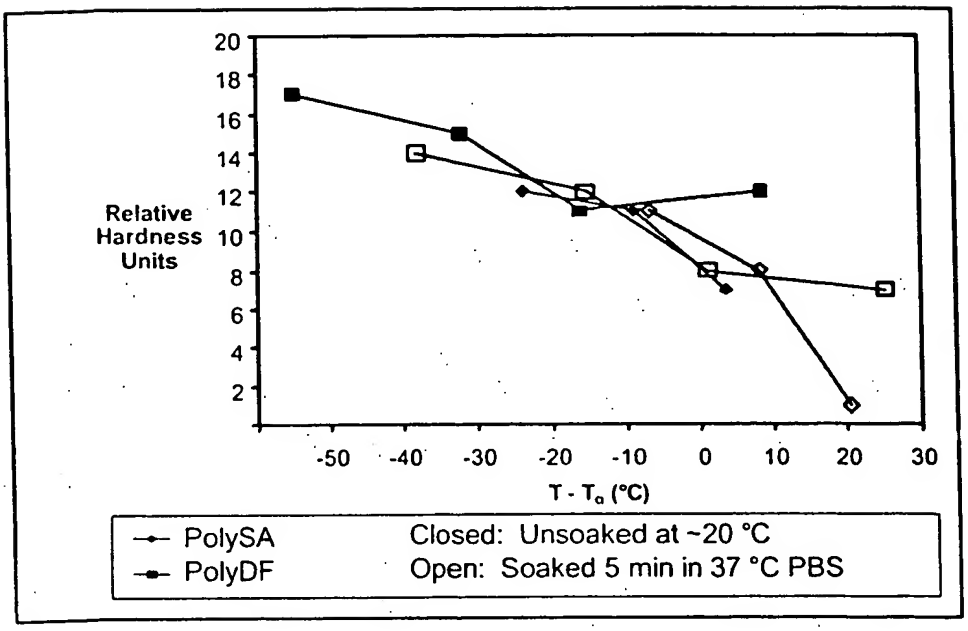

Relative Hardness Units
20
18
16
14
12
10
8
6
4
2
-50
-40
-30
-20
-10
0
10
20
30
T - T$_g$ (°C)
PolySA
PolyDF
Closed: Unsoaked at ~20 °C
Open: Soaked 5 min in 37 °C PBS

FIGURE 54

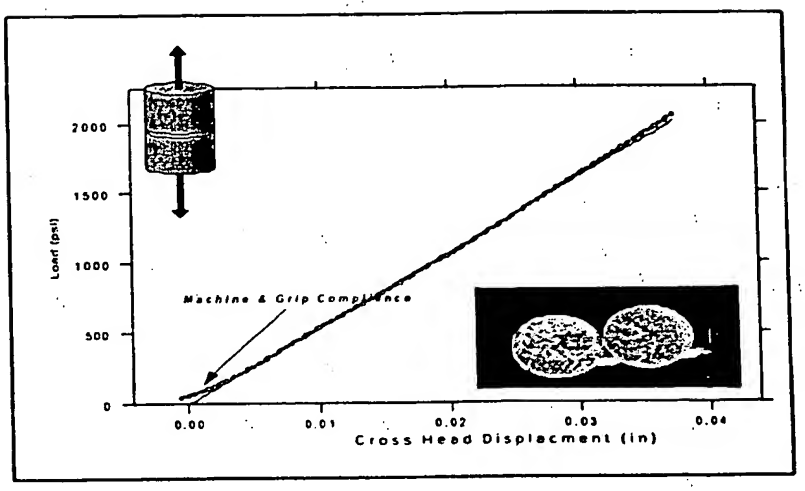

2000
1500
1000
500
0
Load (psi)
Machine & Grip Compliance
0.00
0.01
0.02
0.03
0.04
Cross Head Displacment (in)

FIGURE 55

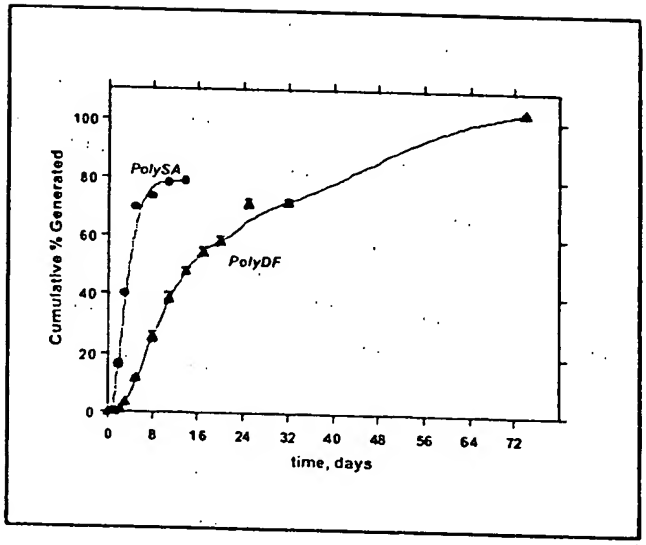

Cumulative % Generated
100
80
60
40
20
0
PolySA
PolyDF
0
8
16
24
32
40
48
56
64
72
time, days

FIGURE 56

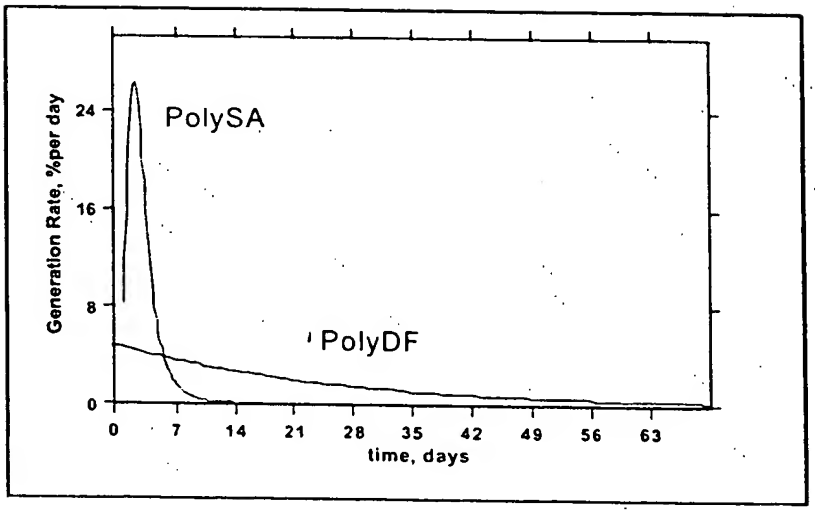

Generation Rate, %per day
24
16
8
0
PolySA
PolyDF
0
7
14
21
28
35
42
49
56
63
time, days

FIGURE 57

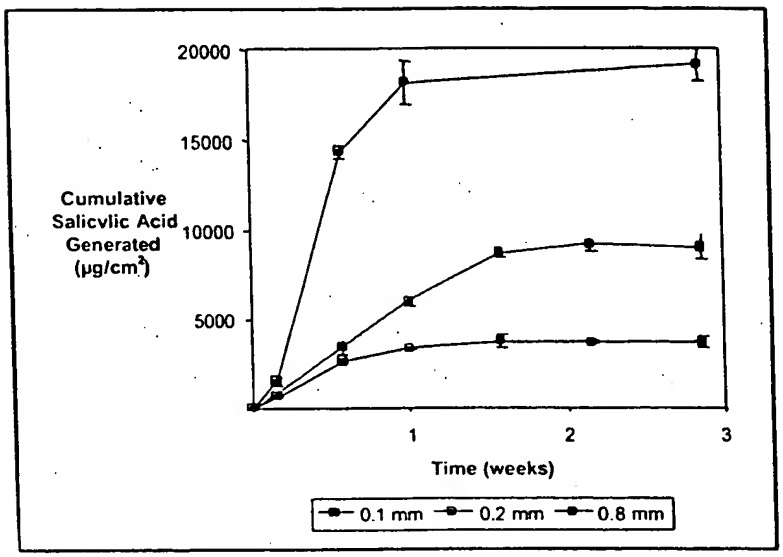

20000
15000
10000
5000
Cumulative Salicylic Acid Generated (µg/cm²)
1
2
3
Time (weeks)
0.1 mm
0.2 mm
0.8 mm

FIGURE 58

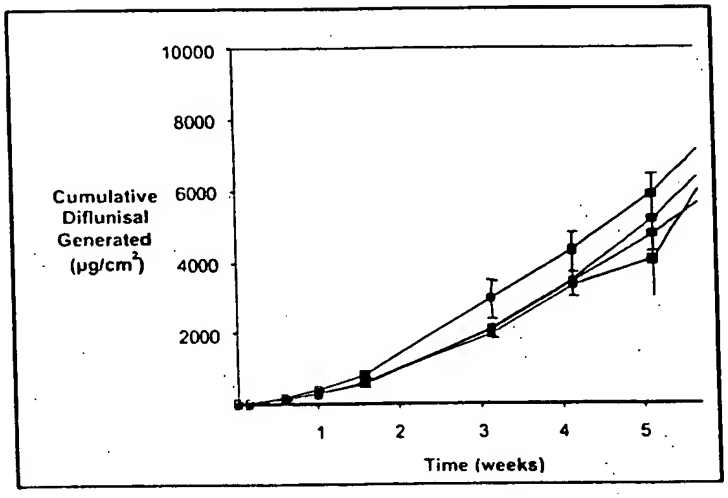

10000
8000
6000
4000
2000
Cumulative Diflunisal Generated (µg/cm²)
1
2
3
4
5
Time (weeks)

FIGURE 59

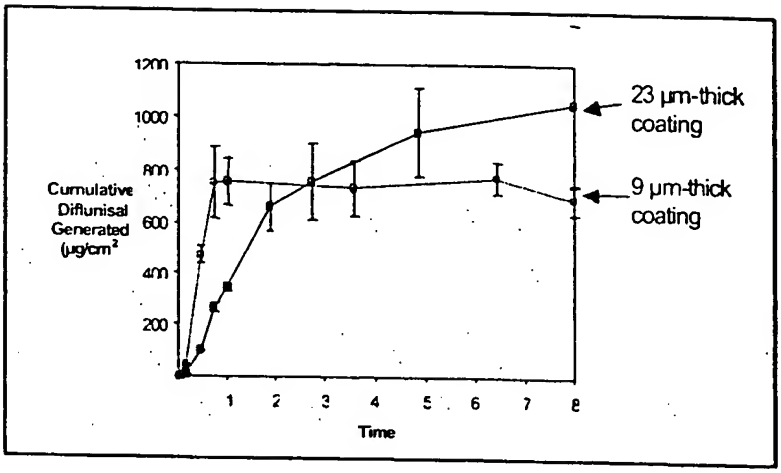

1200
1000
800
600
400
200
Cumulative Diflunisal Generated (µg/cm²)
1
2
3
4
5
6
7
8
Time
23 µm-thick coating
9 µm-thick coating

FIGURE 60

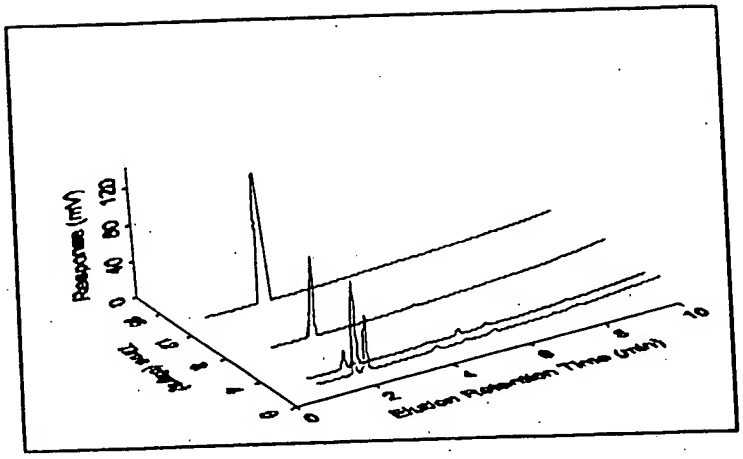


FIGURE 61

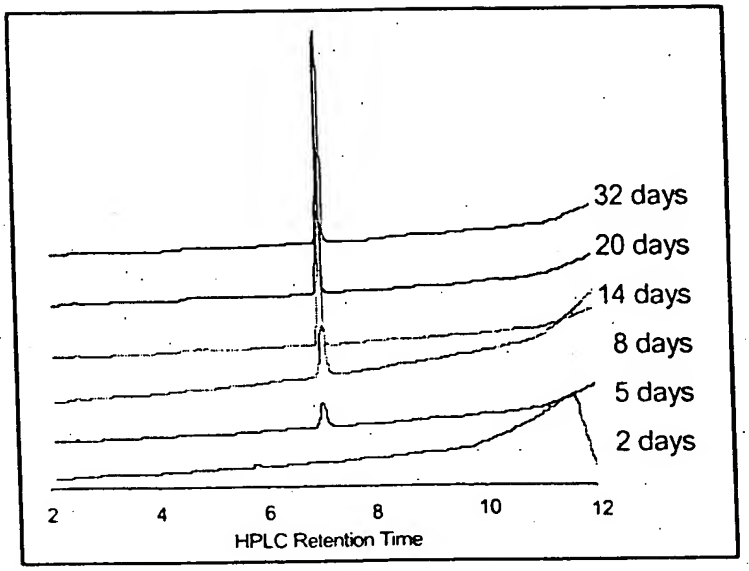

32 days
20 days
14 days
8 days
5 days
2 days
2
4
6
8
10
12
HPLC Retention Time

FIGURE 62

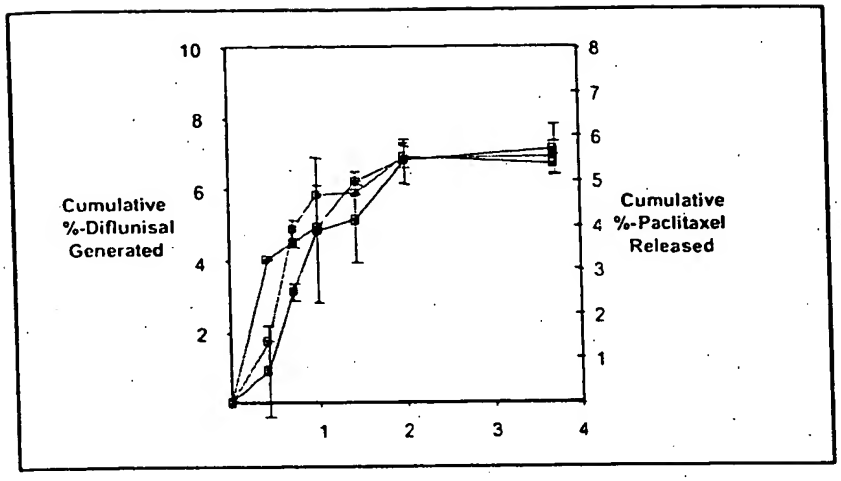

Cumulative %-Diflunisal Generated
Cumulative %-Paclitaxel Released
10
8
6
4
2
8
7
6
5
4
3
2
1
1
2
3
4

FIGURE 63

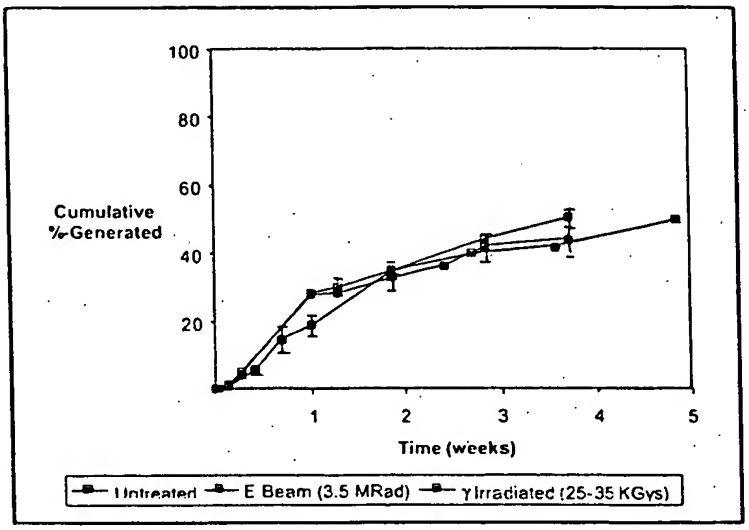

100
80
60
40
20
Cumulative
%-Generated
1
2
3
4
5
Time (weeks)
Untreated
E Beam (3.5 MRad)
γ Irradiated (25-35 KGys)

FIGURE 64

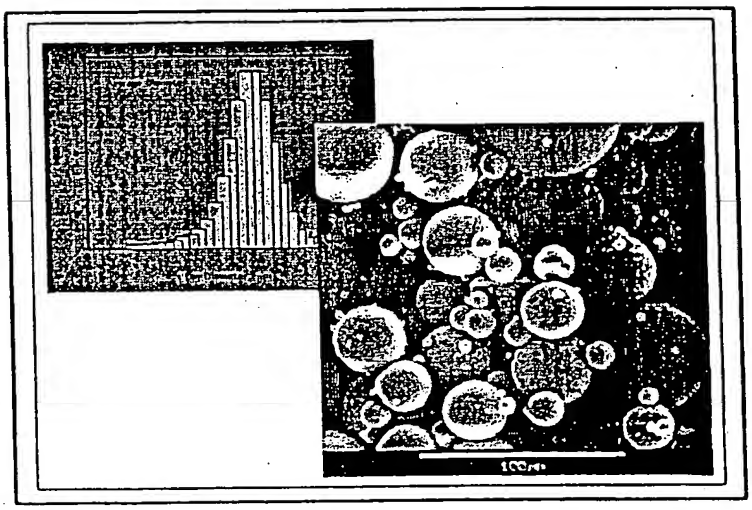


FIGURE 65

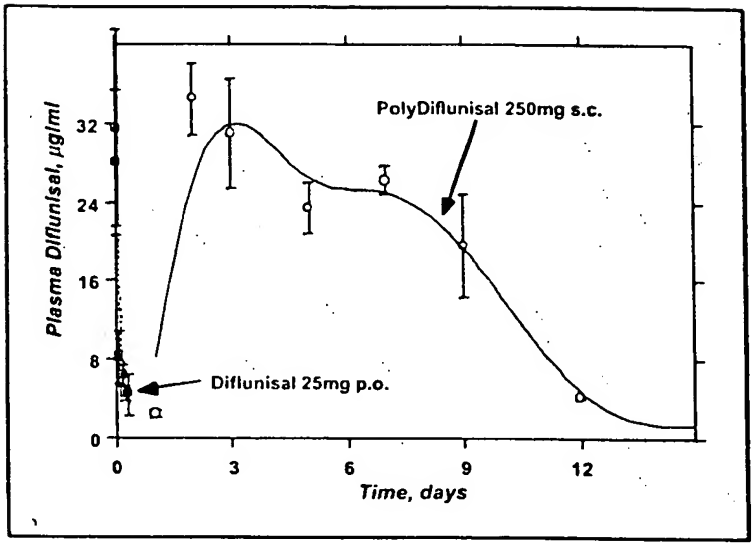

Plasma Diflunisal, µg/ml
32
24
16
8
0
0
3
6
9
12
Time, days
PolyDiflunisal 250mg s.c.
Diflunisal 25mg p.o.

FIGURE 66

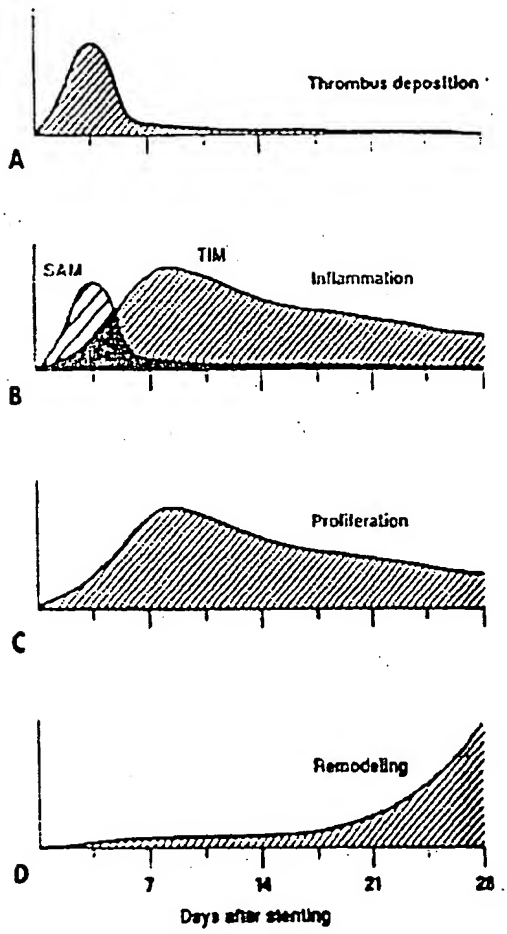

Thrombus deposition
A
SAM
TIM
Inflammation
B
Proliferation
C
Remodeling
D
7
14
21
28
Days after stenting

FIGURE 67

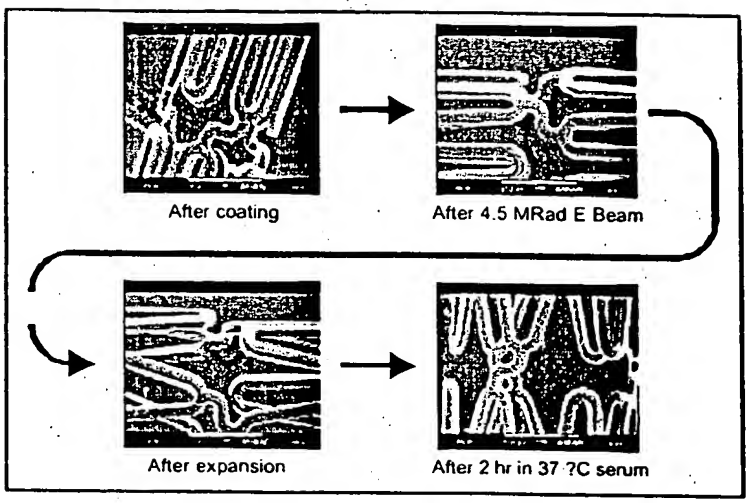

After coating
After 4.5 MRad E Beam
After expansion
After 2 hr in 37 ?C serum

FIGURE 68

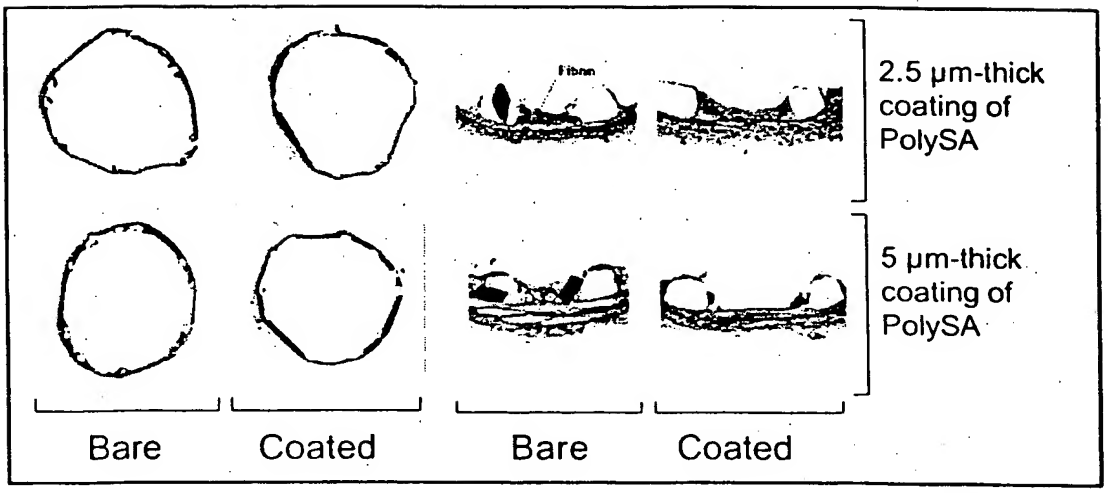

Fibrin
2.5 µm-thick coating of PolySA
5 µm-thick coating of PolySA
Bare
Coated
Bare
Coated

FIGURE 69

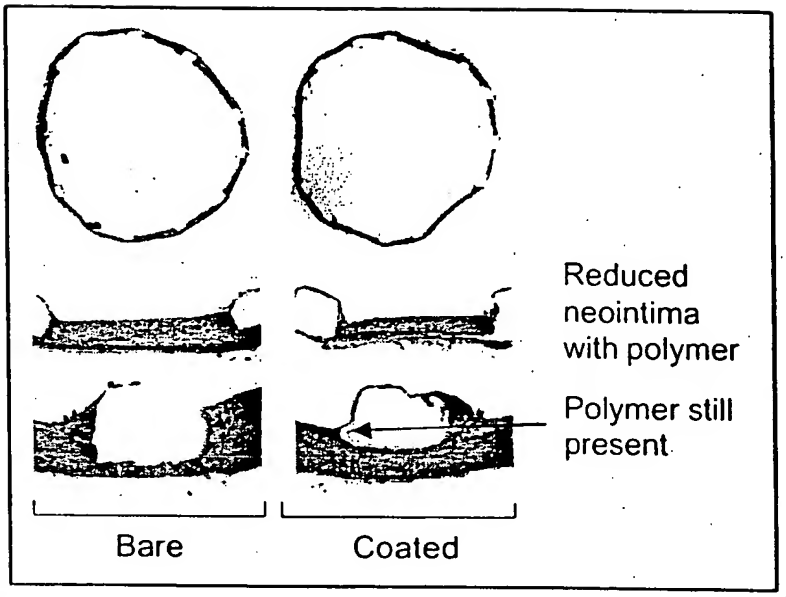

Reduced
neointima
with polymer
Polymer still
present
Bare
Coated

FIGURE 70